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ORIGINAL ARTICLES

PROGRESS IN THE STUDY OF "MUCOVISCIDOSIS" (PANCREATIC FIBROSIS)

With Illustrative Case Presentations

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IN ACCEPTING the first Mead Johnson Award for the year 1949, I should like to thank those who give it and those who have participated with me in the investigation of nutritional disorders, and particularly of the disease pancreatic fibrosis. I should like to acknowledge the assistance received from Dr. Paul R. Patterson who has been associated with me in most of our studies during the past three years.

Dr. May left the Children's Hospital in Boston over three years ago; it is a pleasure to be reunited with him here and to share this honor. Dr. May and I agreed that it would be difficult for us to attempt a presentation which would cover our independent activities. Instead, I should like to thank him for giving me this opportunity to tell you about some of our recent observations at the Children's Hospital. The advantages of working in an institution, in which a vast amount of energy has been expended over a long period of time in the study of pancreatic fibrosis, is quite obvious. The person most responsible for this activity and progress is Dr. Sidney Farber who has clearly presented a theory concerning the nature of the disease which after many years is being generally accepted. In 1941, he was able to refer to an experience of over 150 patients exhibiting the celiac syndrome studied at post mortem over an 18 year period.

Until recently and with rare exceptions all patients with proved pancreatic fibrosis have died. Nevertheless, I should like to suggest that we have much to gain if we discard the prevailing pessimistic attitude toward this disease (pancreatic fibrosis). We may be justified in doing this only if we are prepared to establish a diagnosis early in a given patient and provide that patient with complete medical care. We are all in agreement

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that the outlook is poor when the patient first presents himself with well established bronchiectasis or other far advanced and irreversible lesions.

Figure 1A is that of a 5 month old infant, J.McC., who came to the hospital in February 1947, at which time the diagnosis of pancreatic fibrosis was made. She was under the care of Dr. May for about 4 months until he left Boston. Figure 1B shows this same child three years later, or eight months ago. At present she has far advanced pulmonary changes and her prognosis is poor. Despite good treatment the progression of her disease would have been retarded had the diagnosis been established earlier, and

FIG. 1A. Infant J.McC. B. J.McC. 3 yr. later. FIG. 2. Infant L.C.

had treatment with present day antibiotics been available. If we are to get at these patients earlier, it would be profitable to examine the methods commonly employed in arriving at a diagnosis in relation to the prevailing concept of the disease. That this disease is a generalized one and may involve mucus-secreting glands in different degrees and in different parts of the body was recognized by Farber many years ago, who coined the name, mucoviscidosis.

About a year ago, we made the diagnosis of mucoviscidosis in a 3½ year old child, L.C. (see Fig. 2), who had been followed in our bronchiectasis clinic. In December

1948, at the age of 2½ years, she had sufficient pulmonary symptoms to suggest the possibility of mucoviscidosis, and was accordingly subjected to the procedure of duodenal intubation. Her duodenal fluid contained a normal amount of trypsin but showed marked increase in viscosity as determined by the Ostwald viscosimeter. Because of the finding of normal trypsin, the diagnosis of pancreatic fibrosis was ruled out. It was this increased viscosity which led Dr. Patterson to repeat the duodenal intubation in November of 1949, and again the finding of markedly increased viscosity was noted, with a slight reduction in the tryptic activity, as compared with the previous determination. The findings are demonstrated in table 1.

During this interval a similar patient, P.J., came to postmortem examination, one in whom the duodenal fluid showed normal tryptic activity yet had an increased viscosity. The postmortem examination demonstrated the typical changes of pancreatic fibrosis.

TABLE 1

DUODENAL FLUID
TRYPSIN AND VISCOSITY

Dilution	Undiluted					1/10								1/100			Viscosity
Volume ml.	1.0	.8	.6	.4	.2	1.6	1.4	1.2	1.0	.8	.6	.4	.2	1.0	.5	.25	Time in sec.
Normal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0 or +	0	<180
Pt. L.C.																	
Oct. 1948	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0	0	415
Nov. 1949	+	+	+	+	+	+	+	+	+	+	+	+	0	0	0	0	T. V.*
	+	+	+	+	+	+	+	+	+	+	+	0	0	0	0	0	T. V.

* T. V. = "too viscid to determine."

In the light of our failure to make a correct antemortem diagnosis in Patient P.J., we wondered in retrospect about the significance of the increased duodenal fluid viscosity in establishing the diagnosis of pancreatic fibrosis. In the case of Patient L.C., who died in December 1949, our clinical impression of pancreatic fibrosis was substantiated by the postmortem findings. We have since had a number of similar clinical experiences in which the disease appeared to involve the respiratory tract to a much greater extent than the pancreas. In these instances the examination of the duodenal fluid may show normal tryptic activity, a finding which heretofore has excluded the disease. Fortunately the measurement of the viscosity has proved of value in these selected patients. During the past three years the viscosity of the duodenal fluid has been measured routinely and in approximately 90% of patients with this disease the viscosity is increased to a significant degree.

Another observation which I should like to mention at this time is the laboratory demonstration of progressive loss of tryptic activity of the duodenal fluid in patients suspected of having this disease clinically. Table 2 demonstrates what happened to patient M.H.* in a three months' period during which a significant loss of tryptic activity occurred. Dr. Patterson and I observed this sequence in several other patients. We char-

* Patient referred by Dr. Allan B. Stimson.

TABLE 2

PROGRESSION OF DISEASE
DUODENAL FLUID
TRYPSIN AND VISCOSITY

Dilution	Undiluted					1/10								1/100			Viscosity
Volume ml.	1.0	.8	.6	.4	.2	1.6	1.4	1.2	1.0	.8	.6	.4	.2	1.0	.5	.25	Time in sec.
Normal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0 or +	0	<180
Pt. M.H. 3½ mo.																	
Jan. 1950	+	+	+	+	+	+	+	+	+	+	+	0	0	0	0	0	300
Mar. 1950	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	T. V.*

* T. V. = "too viscid to determine."

acterized some of these individuals as having partial pancreatic insufficiency during the early phase of their illness. They present challenging diagnostic problems which may require serial duodenal fluid examinations for solution. In this category of partial pancreatic insufficiency, a state which may vary considerably in duration in different patients, we often find the protein digestion tests such as the oral gelatin test and the stool trypsin test of little help. In addition, one would not be surprised to find positive nitrogen balance on a normal diet at this time.

In spite of a number of newly devised tests which measure duodenal trypsin indirectly, the most reliable diagnostic procedure is still the direct examination of the duodenal fluid. The demonstration of absent to markedly reduced trypsin in the duodenal fluid with an increase in viscosity is characteristic of the disease. As pointed out, in some instances we may encounter a patient having a normal or only slightly reduced duodenal trypsin with increased viscosity, or an occasional patient may have complete absence of trypsin with a normal viscosity. In the light of the above, the value of the stool trypsin test has certain limitations, assuming that the stool trypsin in small babies reflects duodenal trypsin activity. Table 3 shows the findings of stool trypsin in 98 patients with mucoviscidosis. In the infant age group, the stool trypsin test was positive on one occasion in more than 16 patients. In this group of 16 are included patients such as the one in whom 22 stool determinations were made with positive findings in two, and negative

TABLE 3

STOOL TRYPSIN IN PATIENTS WITH PANCREATIC FIBROSIS
(Duodenal Fluid Negative for Trypsin)

	No. of cases	Positive trypsin	Negative trypsin
Infants	68	16	52
2– 5 yr.	20	0	20
5–10 yr.	9	0	9
Over 10 yr.	1	0	1
	—	—	—
	98	16	82

stool trypsin in 20 specimens. There are others who had as many as 6 or 7 separate stool examinations with the finding of only one positive specimen with the other 5 or 6 specimens being negative. Perhaps some of these false positive stool tests are due to the presence of potent gelatin-liquefying bacteria, as pointed out by Johnstone and Neter.

TABLE 4

NUTRITIONAL DISORDERS: ASSAY OF DUODENAL FLUID AND STOOL FOR TRYPSIN IN 102 PATIENTS

	Duodenal fluid	Stools	
	Positive	Positive	Negative
Infants	80	73	7 (3+)
2– 5 yr.	16	11	5(2+)
5–10 yr.	3	2	1
Adults	3	2	1

The presence of reduced duodenal trypsin in a few patients having partial pancreatic insufficiency may in part explain some of these results.

Dr. Patterson and I have also compared the stool trypsin findings in patients with nutritional disorders who were found to have normal duodenal trypsin. In table 4, one notes that there are seven infants in the total of 80 in whom a negative stool trypsin was obtained at the time the duodenal fluid was found to contain normal amounts of trypsin. Three of these seven patients had positive tests in addition to the one negative test, and are included. The use of a laxative in these patients with negative stool trypsin to hasten the passage of the duodenal contents was not attempted, although this procedure in the past has proved helpful in individual instances.

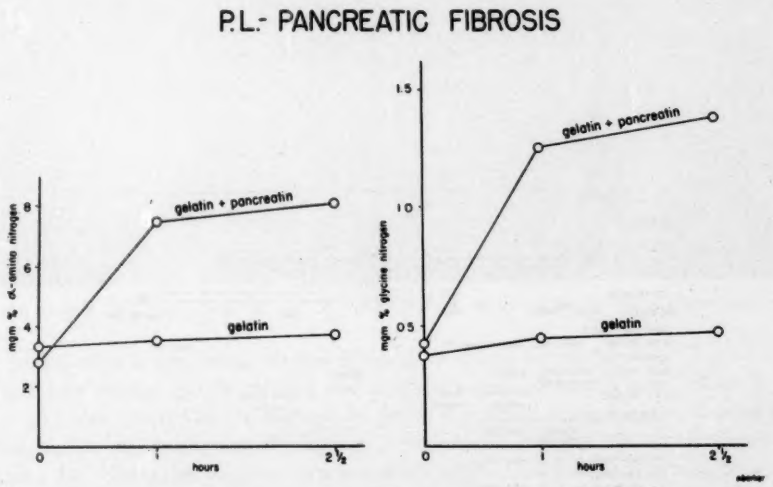

CHART 1

TABLE 5

PANCREATIC FIBROSIS THERAPY

1. High Caloric Diet (Liberal with Exception of Excess Fat)
   Protein Hydrolysates in Small Babies
2. Antibiotics
   Aureomycin, Terramycin, Drugs of Choice
3. Pancreatin
4. High Vitamin Intake

I should like to show chart 1 which was made in collaboration with Dr. Halvor N. Christensen. The therapeutic implication that pancreatin aids in the digestion of protein in patients with mucoviscidosis is clear. Patient P.L. was given a gelatin meal and the alpha amino nitrogen and the glycine nitrogen were determined at fasting and at 1 and at 2½ hours after the test meal. The lower line on the chart shows an insignificant rise in the alpha amino nitrogen or glycine nitrogen of the plasma. When the same test meal was repeated with the addition of pancreatin, a significant rise occurred in the plasma at 1 hour and at 2½ hours.

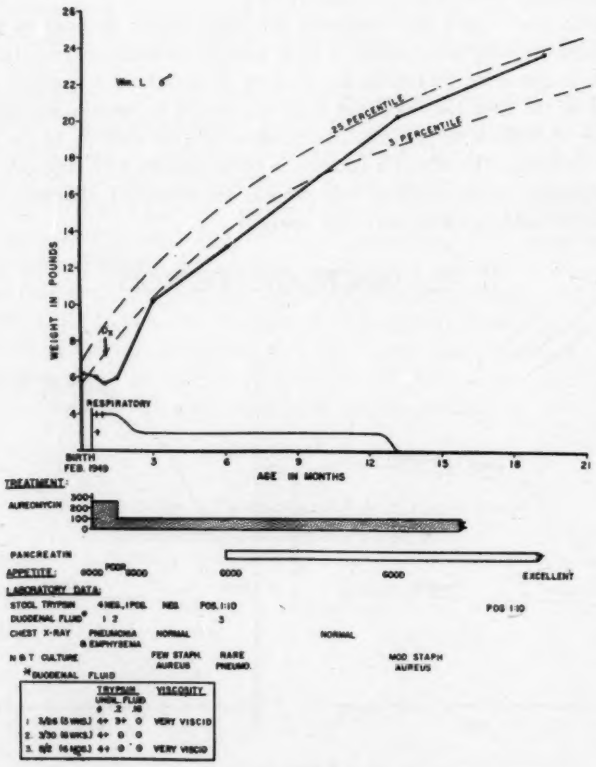

CHART 2

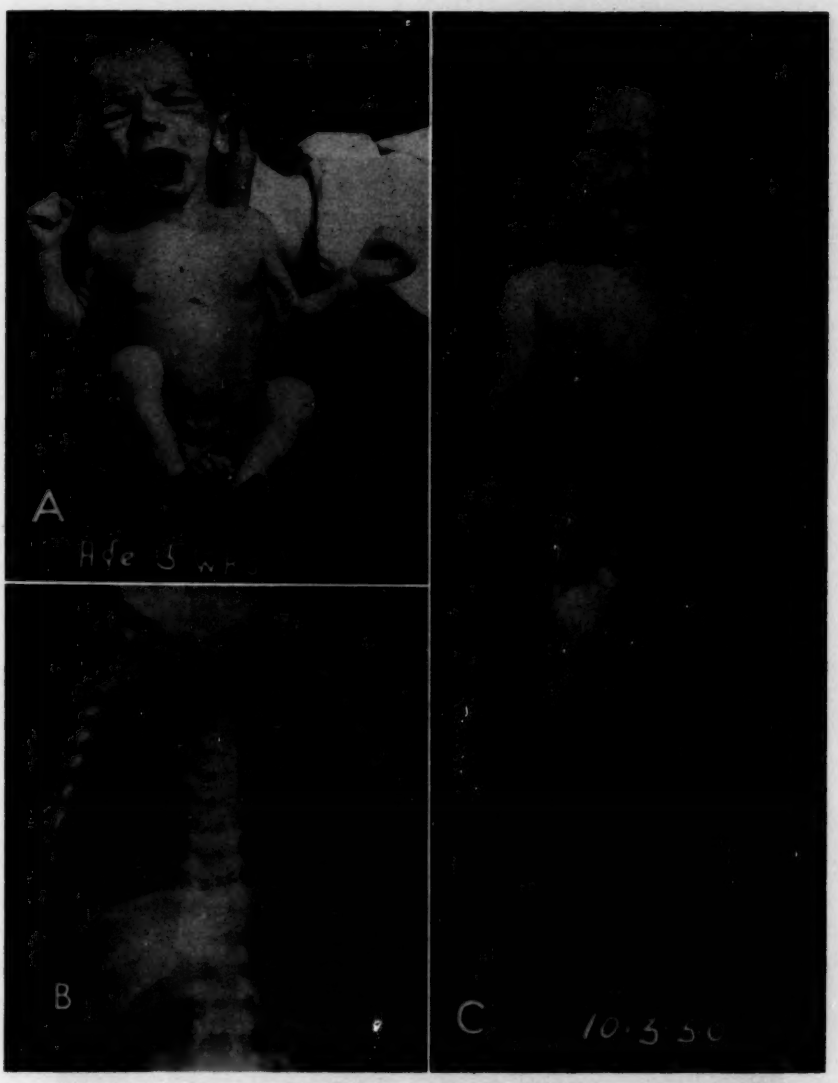

FIG. 3A. Infant W.L. at 5 wk. of age. B. Chest RG of Infant W.L. C. W.L. after treatment.

A brief outline of our present method of therapy is shown in table 5.

I will now present specific patients who illustrate aspects of management. Infant W.L. (Fig. 3A) was referred by Dr. Richard M. Smith at 5 weeks of age because of bronchopneumonia. A roentgenogram of his chest is reproduced in figure 3B. On the basis of this film, Dr. Neuhauser suggested the possibility of pancreatic fibrosis because of small areas of atalectasis and emphysema. Accordingly, a duodenal intubation was carried out, and the patient was found to have a very viscid fluid with no trypsin present in 0.16 ml.

of fluid. Four days later a repeat duodenal intubation was done with essentially the same findings. Five stools were examined during this period and four were negative for trypsin and one was found positive. Chart 2 depicts the course of this child. In spite of the continuous aureomycin therapy he still had staphylococcus aureus in his nasopharynx. His

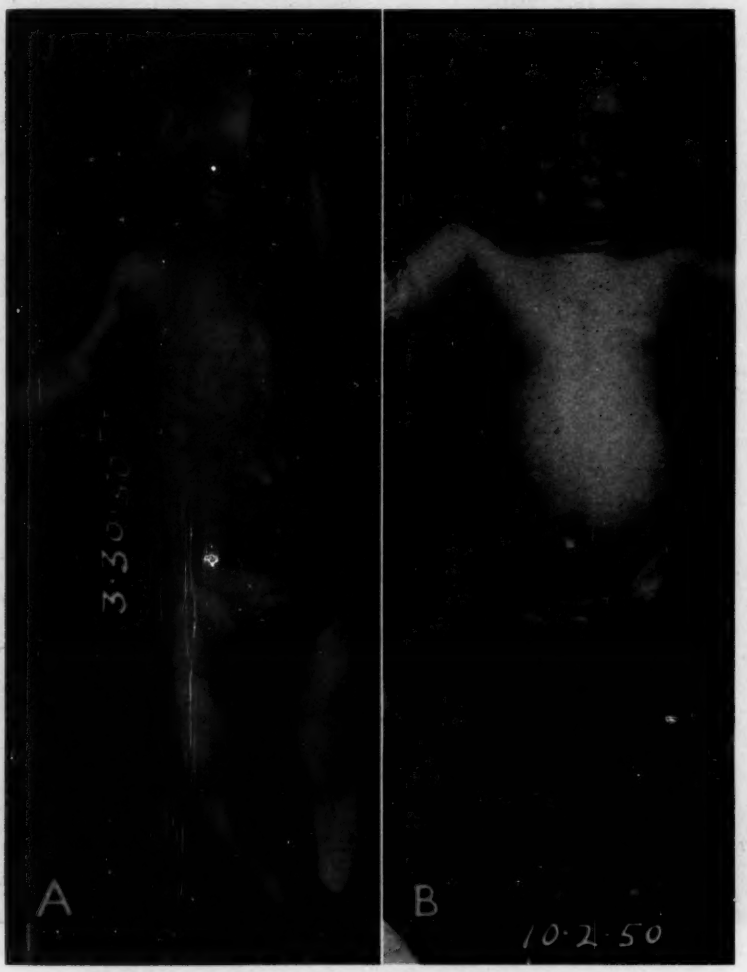

FIG. 4A. Infant S.McP., 3½ mo. of age. B. S.McP., 10½ mo. of age.

respiratory symptoms improved rapidly, and aureomycin was continued in a dose of 100 mg. daily until approximately one month after complete cessation of mild respiratory symptoms. His weight gain was quite striking and he is up to the 25 percentile line at present (see Fig. 3C).

Our present philosophy is to continue the antibiotic therapy for relatively long periods

with occasional short periods of freedom. We have not detected any serious deleterious effect to date with prolonged aureomycin therapy.

Infant S. McP., another patient I should like to discuss, is shown in figure 4A. At 3½ months of age, he was first referred to Dr. R. Cannon Eley who made the diagnosis of pancreatic fibrosis and referred him for study. One sibling died with pancreatic fibrosis. Chart 3 presents most of the pertinent data. He weighed 4.1 kg. at birth, and at the age of 3½ months he weighed approximately 0.9 kg. more than his birth weight. At 1

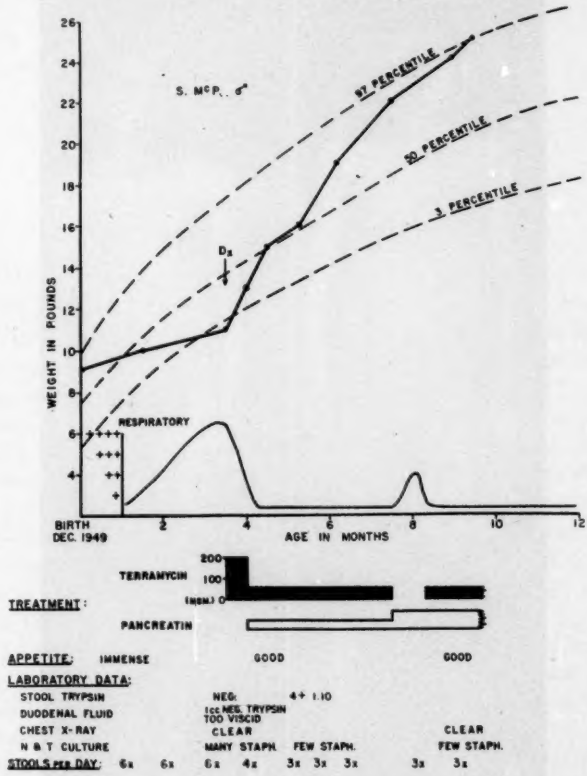

CHART 3

month of age he began to cough and this had increased in severity so that he coughed almost constantly. He averaged six stools per day. He was started on terramycin and within a week his cough showed a striking improvement. Weight gain started with the institution of terramycin therapy and has steadily progressed so that he reached the 97 percentile at the age of about 9 months. Pancreatin was begun approximately one week after the institution of terramycin. Associated with the administration of pancreatin, the appetite, although still very good, seemed to diminish slightly. Some of the pertinent laboratory data reveals a negative stool trypsin before pancreatin therapy, and a positive stool trypsin in the 1/10 dilution after pancreatin therapy was begun. The duodenal fluid revealed no trypsin in 1 ml. of undiluted duodenal fluid, and the fluid was too viscid

to measure in the Ostwald viscosimeter. Here again, although this patient was continued on terramycin the nasopharyngeal cultures still grew out Staphylococcus aureus. In an attempt to determine the effect of omitting antibiotics at the age of 7½ months, the patient began to cough and it was considered best to resume therapy, with a dose of 50 mg./day. His appearance when last seen at the age of 10½ months is shown in figure 4B.

I should like to point out that some patients with this disease are misdiagnosed and

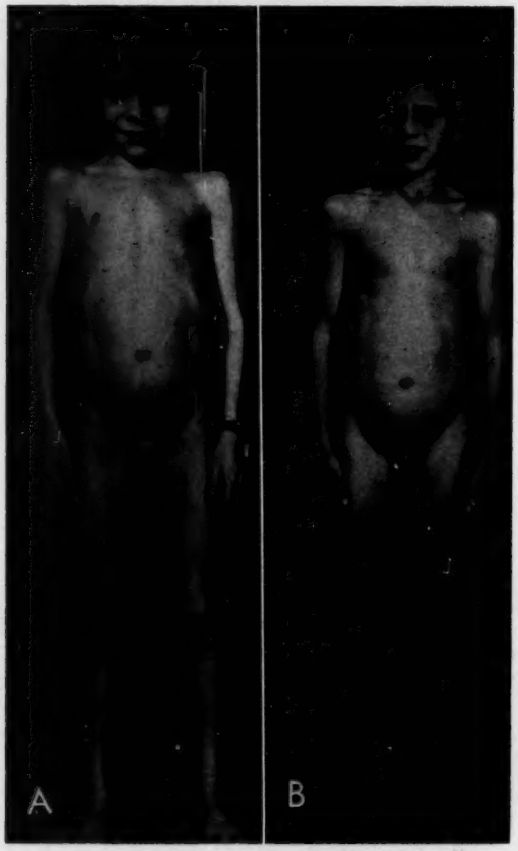

FIG. 5A. E.E., aged 8 7/12 yr. B. E.E., aged 10 11/12 yr.

may be thought to have idiopathic celiac disease. One such patient, E.E. (Fig. 5A), was first seen by us at 8 7/12 yr. He had been treated with a celiac type of diet and with a variety of antibiotics whenever the occasion arose because of respiratory infections. Duodenal intubation was carried out, and the duodenal fluid was viscid and contained no trypsin. He was given continuous aureomycin and a striking improvement in his general well being took place. His chronic respiratory embarrassment which prevented him from joining his playmates was markedly reduced. He was now able to ride a bicycle and participate in vigorous physical activities. His entire mental outlook altered. He was

TABLE 6

RESULTS OF AUREOMYCIN THERAPY

Cases	50	
Age Range	5 wk. to 12 yr. 50% of cases over 2 yr. of age	
Onset of Pulmonary Symptoms	Under 3 mo.	27 cases
	Between 3 mo.–2 yr.	15 cases
	Over 2 yr.	8 cases
Condition when Aureomycin Started	Very poor	9 cases
	Poor	21 cases
	Fair	13 cases
	Good	7 cases
Dose	20–30 mg./kg./day, given in 1 or 2 doses	
Results	Excellent to good	45 cases
	Unsuccessful	5 cases

able to attend school daily and regularly for the first time in his life. His appearance at the age of 10 11/12 years is shown in figure 5B. Of interest from the bacteriologic aspect is the recovery of a strain of Staphylococcus aureus from his nasopharynx that was dependent upon streptomycin for its growth.

In summary, I should like to present the results of aureomycin therapy in a group of approximately 100 patients. Although the last 50 are not tabulated, the findings are essentially the same as in the first 50 so treated (see table 6). The results with terramycin* are equally gratifying and our experience with this drug includes approximately 30 patients.

I should like to conclude my remarks by saying that this disease is more prevalent than is commonly realized, and that much remains to be done in getting at the nature of the basic lesion. I also feel that our colleagues in internal medicine will soon be forced to familiarize themselves with this entity.

In closing I should like to acknowledge the assistance received from a host of associates, all working in close harmony. We can begin with Dr. S. Burt Wolbach and Dr. Kenneth D. Blackfan, and I wish to mention Dr. Dorothy Andersen who led us to the way of the duodenal intubation some 10 years ago. Others to whom I wish to express my appreciation are Dr. Edward B. D. Neuhauser, Dr. M. Wittenborg, Dr. Robert Smith, Dr. Robert E. Gross, Dr. Orvar Swenson, Dr. Charlotte L. Maddock, Dr. Alfred T. Shohl, Dr. Halvor N. Christensen, Dr. Allen C. Crocker, Dr. Charles A. Janeway, Mr. George E. Foley and Dr. Thomas J. Murphy. We are also grateful to the practicing pediatricians who referred patients to us.

Finally, I should like to pay my respects to Dr. Sidney Farber, who provided me with the opportunity of working in this field some 10 years ago and has been a source of stimulation to me ever since.

* Terramycin was supplied by Dr. Gladys Hobby of Chas. Pfizer & Co., Inc., Brooklyn.

SPHEROCYTOSIS AND INCREASED FRAGILITY OCCURRING IN ERYTHROBLASTOSIS FETALIS ASSOCIATED WITH ABO INCOMPATIBILITY

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ALTHOUGH maternal isoimmunization to the Rh antigens will explain the vast majority of cases of erythroblastosis fetalis, rare cases are described occurring in the absence of fetal and maternal Rh incompatibility. Some cases in the latter group have been attributed to isoimmunization to the ABO antigens and although substantial proof of this is lacking in most reported cases, well documented examples have been described.[1, 2] The present report deals with the occurrence of erythroblastosis fetalis in four infants in which the laboratory data strongly support maternal ABO isoimmunization as the causative hemolytic mechanism. In addition to the usual clinical and laboratory findings of hemolytic disease of the newborn infant, each of these patients showed spherocytosis and increased fragility to hypotonic saline during the hemolytic phase of the disease.

ABO Isoimmunization and the Occurrence of Erythroblastosis Fetalis in Infants

The occurrence of isoimmunization in man was first described by Dienst[3] in 1905. He showed that a recently delivered woman of group O might show a rising titre of anti-A or anti-B agglutinin if her infant belonged to group A or B. This observation has been repeatedly confirmed. Boorman et al.[4] showed that there was an increase in maternal anti-A and anti-B titre in over 50% of incompatible matings. Polayes et al.[5] confirmed these high titres in a similar group and concluded, "women with heterospecific pregnancy, who give birth to offspring with neonatal disease simulating erythroblastosis due to Rh immunization, usually show very high anti-A or anti-B isohemagglutinin titres." Wiener[6] and Witebsky[7] demonstrated the existence of immune anti-A and anti-B antibodies and distinguished them from naturally occurring anti-A and anti-B substances.

Unequivocal proof of hemolytic disease due to ABO isoimmunization is usually missing from reported cases and is difficult to obtain for several reasons. The mere finding of a high natural anti-A or anti-B maternal titre during pregnancy has a limited diagnostic value, and frequently occurs with a normal though susceptible offspring. Similarly, immune maternal antibodies are found during pregnancies resulting in normal babies. In addition it is difficult and often impossible to demonstrate adsorbed antibody on the infant's red cells.[8, 9] Wiener[1] was able to demonstrate clumping of saline-suspended red cells in plasma and acacia in one case and Boorman et al.[2] obtained a positive Coombs' test in another case.

In spite of the prevailing confusion about the relative diagnostic significance of anti-

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body titres and the types of antibodies, the consensus is that ABO isoimmunization does not appear to exert any harmful effect on the fetus in the great majority of cases, although rarely it may be associated with hemolytic disease of the newborn infant.

The cases reported below resulted from heterospecific pregnancies, and rising maternal antibody titres were demonstrated after delivery. No maternal Rh antibodies were found. Immune anti-B agglutinins were demonstrated in the sera of two infants who were group B. Immune anti-A agglutinins were demonstrated in another infant who was group A. Although both Coombs' test and albumin tests were negative for adsorbed antibodies, it is believed that in each instance there is strong evidence that the hemolytic mechanism was on the basis of ABO isoimmunization occurring during pregnancy.

Case Reports

Cases 1 and 2 (F twins "A" and "B"): The 1st 2 cases occurred in first born, Negro, nonidentical twin infants.

Maternal and Birth History: There was no family history of erythroblastosis, sickle cell disease or other blood dyscrasia. The mother was a healthy, 21 yr. old, O Rh-positive primigravida. The

TABLE 1

Significant Hematologic Data

	Baby F 'A'				Baby F 'B'				Baby D					Baby S		
Age in Days	2	7	14	21	2	7	14	21	1	3	8	15	22	1	8	15
RBC, millions/cmm.		3.42	3.93	3.03		2.95	3.66	3.45	3.81	3.37	2.01	2.46	3.0	3.85	3.41	3.01
Hgb. gm./100 cc.	11.5	11.0	11.5	8.1	13	9.0	11.0	10.5	14.0	11.0	6.3	7.4	9.0	14.5	11.5	9
Hematocrit									37	32	19.2	24	27	44	34	26
Reticulocytes %		3.4	0.2	0.3		1.6	0	0		3.8	2.8	3.0	1.4	1.9	1.4	2.4
Nucleated RBC/100 WBC	104	4	0	0	26	1	0	0	59	17	2	0	0	170	0	0
Icterus Index										100	15					
Spherocytes	?	yes	0	0	?	yes	yes	0	yes	yes	yes	0	0	yes	yes	0

pregnancy was uncomplicated by any known infection. The mother had not received blood transfusion before pregnancy. The infants were delivered 12 days before the expected date of confinement, without anesthesia, and following an uncomplicated labor of 30 hr. The membranes of the first twin ("A") were ruptured artificially 3 hr. before the spontaneous delivery of the infant from a vertex presentation. The membranes of the second twin ("B") were ruptured artificially 6 min. later, and the infant was delivered by internal version and extraction with forceps to the aftercoming head. Both infants breathed and cried spontaneously within the first few seconds. Manual removal of a small portion of retained placenta complicated an otherwise normal third stage.

Clinical Course: Examination of the infants immediately following delivery was negative except for slight jaundice in Baby "A." Birth weights were 3080 and 2780 gm. in "A" and "B," respectively. The clinical course was afebrile throughout the hospital stay. Formula feedings were well taken from the start, and both infants gained weight steadily. They were alert and active during the first day and appeared normal except for Baby "A" whose jaundice became progressively more intense. During the second day the other twin became jaundiced. Examination at this time revealed splenomegaly in both infants but no hepatomegaly. Hemoglobin determinations on "A" and "B" were 11.5 and 13.0 gm./100 cc., respectively, Baby "A" showing 104 nucleated red cells/100 white cells on the stained smear. Neither of the twins appeared sick during the first week, and except for a moderate degree of lethargy accompanying the jaundice, both infants continued to have good appetites and to gain weight. Jaundice and splenomegaly, more marked in "A," subsided in both twins by the sixth day. The anemia persisted throughout the 30 day hospitalization, and on discharge the hemoglobin determinations were 9.5 and 11.0 gm./100 cc. in "A" and "B," respectively.

Laboratory Data: Hematologic investigation after birth revealed a normocytic and normochromic

TABLE 2

STUDIES OF ERYTHROCYTE FRAGILITY IN HYPOTONIC SALINE

Day Post Partum	Subject	Beginning	Well Marked	Complete
7th	Baby F'A'	0.69*	0.54	0.27
	Baby F'B'	0.69	0.54	0.24
	Infant Control	0.48	0.45	0.30
13th	Baby F'A'	0.51	0.45	0.27
	Baby F'B'	0.51	0.45	0.24
	Infant Control	0.48	0.42	0.27
21st	Baby F'A'	0.48	0.42	0.27
	Baby F'B'	0.48	0.45	0.30
	Adult Control	0.45	0.42	0.33
3rd	Baby D	0.66	0.60	0.24
	Adult Control	0.45	0.42	0.30
8th	Baby D	0.57	0.51	0.33
	Adult Control	0.45	0.42	0.33
15th	Baby D	0.51	0.48	0.33
	Adult Control	0.45	0.42	0.33
29th	Baby D	0.51	0.45	0.33
	Adult Control	0.48	0.45	0.33
1st	Baby S	0.63	0.50	0.25
	Adult Control	0.47	0.45	0.33
14th	Baby S	0.51	0.48	0.33
	Adult Control	0.48	0.45	0.33
21st	Baby S	0.48	0.45	0.27
	Adult Control	0.45	0.42	0.33
55th	Baby S	0.48	0.42	0.32
	Adult Control	0.45	0.42	0.30

* Figures express percentage of NaCl in distilled water.

The routine method described in Wintrobe's *Clinical Hematology* was used in making these determinations.

anemia in both twins with nucleated red cells, spherocytes and reticulocytes on the smear of the peripheral blood. Routine blood studies on the mother showed a simple microcytic anemia but were otherwise normal. These findings are recorded in table 1.

The finding of spherocytes led to an investigation of red cell fragility in hypotonic saline. The results are recorded in table 2 and indicate an increased fragility and increased resistance in both infants with a return to normal values by the third week.

Sickle cell preparations revealed transmission of the sickle cell trait in the family. There was sickling of 25% of the maternal grandmother's red cells in ½ hr. in 2% sodium bisulfite solution, and 25% of the mother's red cells were found to sickle in 24 hr. in the same solution and 95% in 24 hr. in the fresh preparation. Sickling of 20% of Baby "A" 's red cells occurred within 24 hr. in

the fresh preparation, with 10% sickling after the same length of time in 2% sodium bisulfite solution. The trait was absent in the father and Baby "B."

Results of blood group investigations (see table 3) show that the mother and both twins have identical Rh blood groups but there is heterospecificity or incompatibility in the ABO groups. Antibody studies on maternal and infant sera are shown in table 3. Of special interest is the absence of Rh and Hr antibodies in both maternal and infant sera and the rising maternal anti-B titre after delivery. Finally anti-B immune antibodies were present in the serum of Baby "A," but no adsorbed antibody could be demonstrated on the red cells of either infant.

Cultures of the nasopharynx, throat, blood, urine and stools were noncontributory. Serologic tests for syphilis of mother and both twins were negative and roentgenograms of the long bones were normal. Prothrombin estimation, bleeding and clotting times were also within normal limits. Bile was present in the stools at all times. Both infants were secretors of B substance.

Case 3 (Baby D): This white male infant was admitted at 24 hr. of age for investigation of jaundice of 18 hr. duration.

Maternal and Birth History: The mother was a healthy, 33 yr. old, O Rh-positive white multipara. This was her seventh pregnancy. She had an unexplained miscarriage 10 yr. previously during her second pregnancy. It was interesting that her first child was also jaundiced at birth and this subsided spontaneously after 2 wk. None of her subsequent babies were jaundiced during the newborn period until the present one. The mother had never received any blood transfusion in the past.

Except for hypertension the mother's health throughout this pregnancy was considered normal. She had no known infection. The onset of labor was spontaneous at term. There was prolapse of the cord at the end of the second stage and the infant was said to be pale and dyspneic for the first few hours. Birth weight was 3.8 kg. He developed jaundice during the 1st 12 hr. and was referred to this hospital at 24 hr. for further investigation.

Clinical Course: Examination on admission revealed a well nourished, alert and active infant with marked jaundice. He was afebrile and no focus of infection was noted. There was mild edema of the back. The liver edge was palpable 2 cm. below the rib margin. The spleen was not felt. Hgb. 14.0 gm./100 cc. and there were 60 nucleated red cells/100 white cells on the stained smear.

Jaundice subsided markedly by the fourth day and was gone by the end of the first week. The spleen was felt on the fifth day and also disappeared by the end of the first week. He was afebrile, alert and active and gained well throughout the hospital stay, and there was no significant rapid fall in hemoglobin.

Laboratory Data: Hematologic investigations on admission revealed a normochromic normocytic anemia and many nucleated red cells on the stained smear. In addition there was marked spherocytosis, moderate anisocytosis, slight poikilocytosis, moderate polychromatophilia and basophilic stippling of the red cells. These findings are recorded in table 1. Table 2 reveals the changes in red cell fragility in hypotonic saline as noted in the previous cases. Fragility returned to normal by the end of the first month. Results of blood group determinations are shown in table 3. There was no Rh incompatibility although heterospecificity of the ABO group existed. The mother was group O and the infant group A. It was interesting that her first child, who was jaundiced at birth, was also group A although one other child was group A and was apparently never jaundiced. The other children were group B. Antibody studies on maternal and infant sera are shown in table 3. There was a rise in the maternal anti-A antibody titre noted after delivery and immune anti-A agglutinins were demonstrated in the infant's serum and disappeared by the third day. No adsorbed antibody was demonstrated on the infant's red cells.

Cultures of the blood, spinal fluid and stool were negative. Throat and nasopharyngeal cultures were not significant. The serologic tests for syphilis were negative in mother and infant. The prothrombin time was normal. Total bilirubin was 8.2 mg. % with a direct fraction of 0.8 mg. % at birth. The total bilirubin was normal within 3 wk. Cephalin flocculation and thymol turbidity tests were normal. Bile was present in the stool at all times. Chest RGs, abdomen and long bones were negative. Sputum examination revealed the infant to be a nonsecretor.

Case 4 (Baby S): This Negro female infant was noted to have jaundice in the Newborn Nursery during the first day of life.

Maternal and Birth History: The mother was a 43 yr. old healthy multiparous woman who had had 10 previous pregnancies. All her children are well and none of them was jaundiced during the

TABLE 3

BLOOD GROUPS, RH AND ABO ANTIBODIES IN MATERNAL AND INFANT SERA, AND TESTS FOR ADSORBED ANTIBODIES ON INFANTS' RED CELLS

Subject	Days Postpartum	Serum							Cells		Blood Grouping		
		Rh Antibodies			ABO Antibodies						Rh		ABO and MN
		Indirect Antihuman Serum Test at Room Temp. and 37.5° C. (Indirect Coombs)	Circulating Rh and Hr Antibodies (Serum, saline and albumin)	Rh Blocking Antibodies. (Albumin)	Anti-A			Anti-B			Adsorbed Antibodies with Serum, Albumin, and Serum-albumin at Room Temp. and 37.5° C.	Direct Antihuman Serum Test. (Direct Coombs)	Wiener	Fisher	
					Albumin	Serum	Saline	Albumin	Serum	Saline					
Mother F	2	—*	—	—	96†	96	48	76	256	256			Rh_2	cDE	ON
	9		—	—	96	96	96	512	1536	3072					
	14		—	—	192	192	384	8192	24576	6144					
	20				48	48	128	6144	6144	16384					
	36		—	—	384	758	384	16384	3072	16384					
	50		—	—	192	96	192	6144	3072	3072					
	62		—	—	192	384	64	24288	24288	3072					
Father F													Rh_0	cDe	BMN
Baby A	2	—	—	—	48	96	—	—	8	—	—	—	Rh_2	cDE	BMN
	14	—													
	62		—	—				—	—	—		—			
Baby B	2	—	—	—	48	48	—	—	—	—	—	—	Rh_2	cDE	BN
	14														
	62		—	—				—	—	—		—			
Mother D	1		—		512	512	512	64	64	192			Rh_1Hr_1	CDe	OM
	8		—	—	3072	3072	768	96	96	96			Neg.		
	18		—	—	1536	12288	768	64	192	96					
	34				3072	3072	768	384	384	64					
	56														
Father D													Rh_1Hr_1 Pos.	CDe	ABMN
Baby D	1		—		1	1	—	8	1	3	—	—	Rh_1Hr_1	CDe	AMN
	2		—		1	—	—	32	32	1	—	—	Neg.		
	7		—	—	—	—	—	64	16	1	—	—			
	14		—	—	—	—	—				—	—			
Mother S	2		—	—	192	128	384	3072	3072	384			Rh_0	cDe	OMN
	7		—	—	192	192	384	3072	3072	768					
	35				48	48	768	6144	6144						
Baby S	2		—	—	48	48	4	3	24	—	—	—	Rh_0	cDe	BN
	7		—	—	48	48	1	—	1	—	—	—			

* Negative.
† Indicates units of antibody in albumin, serum and saline solution.

newborn period. Her past history was noncontributory. All previous pregnancies went to term and labor was unremarkable except in the penultimate one in 1949 which lasted 2 days. She had received no blood transfusion in the past. This infant was delivered at term and the onset of labor was spontaneous although the first stage lasted 30 hr. The membranes ruptured suddenly and she delivered spontaneously in bed. The immediate condition of the baby was good.

Clinical Course: Examination during the 2nd 12 hr. of life revealed an afebrile, well nourished and well developed infant in no distress. Slight jaundice was noted. The spleen was palpable 2 cm. below the costal margin and the edge of the liver was palpable. Hgb. 16.0 gm./100 cc. and there were many nucleated red cells on the stained smear.

The jaundice subsided by the fifth day and the spleen was palpable for the 1st 2 wk. There was a gradual fall in hemoglobin during the 1st 2 wk., at which time the Hgb. was 10 gm./100 cc. Throughout her hospital stay the infant was well in all respects and gained weight well.

Laboratory Data: Hematologic data are recorded in table 1. It will be seen that there was a normocytic normochromic anemia, and many nucleated red cells were seen on the peripheral smear. There was marked spherocytosis, marked anisocytosis, slight poikilocytosis and moderate polychromatophilia. Spherocytosis disappeared by the end of the first week. The changes in fragility were again noted and are recorded in table 2. Fragility returned to normal at the end of the third week.

The results of blood grouping and antibody testing are shown in table 3. Again there was no Rh incompatibility but there was ABO heterospecificity. The mother was group O and the infant was group B. No Rh antibodies were found. Anti-B immune agglutinins were demonstrated in the infant's serum at birth and tests for adsorbed antibodies were negative.

Unfortunately, it was impossible to obtain blood from the mother, the infant and other members of the family for further investigation.

Treatment

The anemia in all four cases was mild and exchange transfusion was not deemed necessary. Small frequent transfusions were given as indicated by the hemoglobin estimation. O Rh-positive blood was used because of the absence of the A and B antigens and hence intravascular agglutination was precluded.

During the first few days of life streptomycin and penicillin were administered to combat any intrauterine acquired infection. In all infants antibiotics were discontinued at the end of the first week.

Discussion

The occurrence of erythroblastosis, anemia and jaundice during the first day of life suggested several possibilities. Rh isoimmunization was excluded by the absence of maternal Rh antibodies and negative tests on infants' red cells for adsorbed antibodies. However, analysis of the ABO groups of the mother and infants indicated the possibility of ABO incompatibility in each case. Intrauterine infection was excluded by negative cultures and failure of the mothers to show signs of infection. Syphilis was excluded by negative maternal and infant serologic tests and normal long bones by roentgenogram. It was not possible to investigate viral infection as suggested by Cappell and McFarlanes' cases.[10] Congenital familial hemolytic jaundice has been described in the newborn infant,[4] and the occurrence of spherocytosis and increased fragility suggested this possibility. However, disappearance of spherocytosis and return to normal fragility in the first month did not support this concept. In one of the mothers (Mrs. D), there was a temporary increase in fragility and the exclusion of familial hemolytic jaundice was delayed. Further studies on the maternal fragility in hypotonic saline in similar cases are being done.[11] Familial nonhemolytic jaundice can be seen in the first day of life but was ex-

cluded by the subsidence of jaundice during the first weeks of life. Physiologic and obstructive jaundice were not seriously considered because of the early appearance of jaundice. Likewise, the sickle cell trait was believed to be merely a coincidental finding in the twins and did not play any etiologic role in their anemias.

Although the tests for adsorbed antibodies were negative, and unequivocal proof of ABO isoimmunization as the cause of the hemolytic disease is thus lacking,[12] there is strong evidence to support the latter diagnosis. First, ABO heterospecificity and a postnatal rise of the appropriate maternal immune antibody titre was present in each case. In addition, an immune antibody corresponding to the maternal immune antibody was demonstrated in one of the twins and in both of the other infants' sera. It seems reasonable to attribute this finding to transplacental transfer. While the latter immune antibodies may be present in the offspring of heterospecific pregnancies in the absence of clinical erythroblastosis fetalis, the authors believe that considerable etiologic importance can be attached to their presence in these cases.

Dameshek and Schwartz[13] in 1937 reported three cases of acute hemolytic anemia in adults. They demonstrated a hemolysin in the sera of two of the patients and reported the finding of spherocytosis and increased fragility as well. They introduced a new concept that a spherocyte is a red cell injured by a hemolytic agent and opposed the prevailing view that it is an inherited bone marrow defect of red cell production. Later, Dameshek suggested that a similar mechanism is operative in hemolytic states due to isoagglutinins anti-A, anti-B and anti-Rh.[14]

The present investigators have been unable to find similar observations in the reported cases of hemolytic disease due to ABO isoimmunization. Diamond,[15] in discussing erythroblastosis fetalis due to Rh antigens, says "the fragility of red cells in hypotonic saline shows slight increase in the concentration at which hemolysis begins and a decrease at its termination, a state usually described as increased resistance." There is no mention of spherocytosis on the stained smear of the peripheral blood.

It is interesting that in the cases reported here and those described by Dameshek et al. there was spherocytosis and increased red cell fragility in hypotonic saline associated with an abnormal antibody in the sera. The hemolytic mechanism suggested by Dameshek for hemolytic anemias in adults might also explain the finding of spherocytosis and increased erythrocyte fragility, the circulating immune anti-A and anti-B antibody acting as the hemolysin. The demonstration of spherocytosis and altered hypotonic fragility of the red cells associated with an ABO incompatible pregnancy may be further evidence of diagnostic value in cases of hemolytic disease of the newborn infant.

Summary

Four cases of hemolytic disease of the newborn infant are reported. There was ABO incompatibility and high maternal immune antibody titre after delivery. Immune antibody was demonstrated in the sera of 3 of the 4 infants.

The difficulties in making an unequivocal diagnosis are discussed and the diagnostic value of immune antibody in the infant's serum is emphasized.

The presence of spherocytosis and altered erythrocyte hypotonic fragility during the hemolytic phase is noted. These findings are similar to cases of acute hemolytic anemia in adults previously reported.

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SPANISH ABSTRACT

Ocurrencia de Esferocitosis y Aumento de Fragilidad Capilar en Eritroblastosis Fetalis Asociada con Incompatibilidad Sanguinea ABO

Se reportan cuatro casos de eritroblastosis fetalis secundaria a la iso-inmunizacion sanguinea materna (grupos ABO). En cada caso, se demostró la presencia de esferocitosis con aumento de fragilidad capilar a la solución salina hipotonica durante la fase hemolitica.

Estos casos se caracterizaron clinicamente por la presencia de anemia, ictericia, esplenomegalia, y hepatomegalia. El cuadro sanguineo demostró aumento de las celulas rojas nucleadas (normoblastos) y reticulocitosis. Ningún caso demostró incompatibilidad a los factores Rh o Hr.

Los signos sugestivos de iso-inmunizacion ABO fueron el aumento post-natal de la concentración de anticuerpos maternos en questión, y la presencia de anticuerpos inmunes en el suero de tres de los cuatro niños reportados. La esferocitosis y el aumento de la fragilidad capilar a la solución salina hipotonica ocurrió en los cuatro casos. La fragilidad capilar persistió mas tiempo que la esferocitosis.

Cada paciente requirió solamente una pequeña tranfusión de sangre.

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ACUTE HEMOLYTIC ANEMIA RELATED TO NAPHTHALENE

Report of a Case in a Newborn Infant

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ACUTE hemolytic anemia in the newborn infant is, except in erythroblastosis fetalis, extremely rare. A premature infant has been reported as having hemolytic anemia[1] but critical analysis suggests megaloblastic anemia clinically, hematologically and therapeutically.

Congenital hemolytic icterus, sickle cell anemia and Mediterranean anemia rarely become apparent in the neonatal period[2] and no report has been made of an acute hemolytic crisis of one of these chronic diseases in a newborn infant. Nursing mothers have transmitted favism to infants.[3] Mismatched transfusions, infections, especially with hemolytic streptococci and Clostridium welchii, and infestations with malaria may be responsible for acute hemolytic manifestations. Various chemical agents may also produce this picture, although no previous case has been reported in a newborn infant. Other forms with an abrupt onset of hemolytic anemia without any demonstrable cause are grouped together as "Lederer's anemia."

This report presents the clinical and pathologic findings in a case of hemolytic anemia due apparently to naphthalene poisoning.

CASE REPORT

Clinical Findings: S. J., a 6 day old female infant, was admitted to the hospital because of jaundice and cyanosis of several hours' duration. The infant was a full-term baby; delivery was normal and she had no trouble in the hospital. The diapers were not stamped with dye. She was breast fed for 3 days with 2 supplemental feedings of evaporated milk, karo and water. No well water was used. On the 3rd day the mother's breasts felt sore and her nipples bled slightly; but she had no fever or other symptoms while nursing the baby. The only solutions used on the breasts were boric acid and olive oil, and there was no history of ingestion of fava beans. The only medications used on the infant were baby powder and baby oil. The mother stated, however, that the diapers used had been stored in moth balls and moth crystals, and although rinsed before using, they still "reeked" of moth balls.

There was no family history of anemia, tuberculosis or malaria. No relative had an Italian, Greek or other Mediterranean racial background. The mother had taken no drugs, except for 2 tablespoons of milk of magnesia and 6 to 10 drops of cascara aromatic for constipation on the 4th day postpartum. Both parents had negative serology for syphilis. A 3 mo. old male sibling died of congenital heart disease.

Physical examination revealed a moderately cyanotic and moderately icteric newborn female. The cyanosis appeared to increase on crying. A loud systolic murmur was heard along the left sternal border and was transmitted to the back. The liver was 3 cm. below the right costal margin. The spleen edge was just palpable. On rectal examination a brown stool with a small amount of what appeared to be black meconium stool was found. Otherwise, the physical examination was negative.

Laboratory studies: On admission, Hgb. was 19.8 gm./100 cc. or 126% and decreased to 9.0 gm./100 cc. or 57% with RBC 2.40 million/cmm. by the 3rd hospital day. On admission WBC was

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18.0 thousand/cmm. with 57% neutrophils, 32% lymphocytes, 5% monocytes, 3% eosinophils and 5% metamyelocytes. There were 5 normoblasts/100 white blood cells. The Coombs' test was negative on 2 occasions. NPN was 45 mg./100 cc., and the van den Bergh was 1.2 mg./100 cc. direct, 12.8 mg./100 cc. indirect. Both the Kline and Kahn tests were negative. The patient's blood type was 0, Rh-negative. Thymol turbidity was 2 units and cephalin flocculation 2+. Blood cultures drawn on admission and on the 3rd hospital day were both negative. The urinary albumin was 4+, sugar and acetone were absent and the pH was 7.5. Microscopic examination of the urine showed 12 WBC/high power field, 12 to 14 RBC/high power field, 5 to 8 coarsely granular casts/high power field and occasional finely granular casts. Chest roentgenograms and long bones were negative.

Clinical course: Before the results of laboratory tests were known, it was thought that the infant had congenital heart disease with physiologic icterus; she was therefore placed in oxygen. The original blood count and a chest RG were not remarkable. After the preliminary blood culture was drawn, penicillin was started. The urine was amber-colored the 1st 2 days, then it became a dark reddish-brown and was found to contain hemoglobin. On the 3rd hospital day, the blood hemoglobin dropped and the child appeared critically ill. She was kept warm. Plasma and whole blood were given to combat shock. Caffeine and sodium benzoate were given for stimulation. For a few hours she appeared improved; thereafter the course was steadily downhill and she died on the 4th hospital day.

Autopsy (only positive findings given): The lungs showed small foci of atelectasis; occasional bronchioles and alveoli contained aspirated material. Also a few small focal hemorrhages were present. The liver weighed 178 gm. (normal weight 123 gm.), and the spleen weighed 20 gm. (normal weight 10 gm.) There was a tiny accessory spleen. Extramedullary hematopoiesis was found in the heart, liver, spleen and adrenals. Hemoglobin deposits in the kidneys were evident grossly, and microscopically were seen in the collecting tubules. There were some petechial hemorrhages in the urinary bladder. Chemical and spectrophotometric examinations of blood and urine taken immediately post mortem revealed large amounts of methemalbumin* in the serum and urine.

Subsequent blood studies of the parents gave the following results:

Mother: Blood type: O MM cde/cde.

Rh antibodies: Agglutinin titer negative (each repeated twice).

Hgb. 13.6 gm./100 cc. or 87%; RBC 4.60 million/cmm. Packed cell volume 43%. WBC 10.4 thousand/cmm. with 67% neutrophils, 27% lymphocytes, 4% monocytes and 2% eosinophils. Platelets appeared normal. Fragility test: beginning hemolysis, 0.48; end of hemolysis, 0.38.

Father: Blood type: O MM cde/cde (repeated twice).

Hemoglobin 16.7 gm./100 cc. or 107%; RBC 5.56 million/cmm. Packed cell volume 41%. WBC 10.3 thousand/cmm. with 57% neutrophils, 31% lymphocytes, 6% monocytes, 4% eosinophils and 2% basophils. Platelets appeared normal. Fragility test: beginning hemolysis, 0.50; end of hemolysis, 0.38.

Discussion

It is felt that acute hemolytic anemia due to infectious agents, vegetable and animal poisons, mismatched transfusion, hemolysins of the immune-body type, an acute exacerbation of chronic hemolytic anemia, and chemical agents, outlined by Wintrobe,[4] have been ruled out by suitable criteria. Recently naphthalene has been proved to be a cause of serious acute hemolytic anemia. Zuelzer and Apt[5, 6] reported four cases of fulminating hemolytic anemia in young children who had either swallowed or merely sucked on a mothball. They produced hemolytic anemia in animals with naphthalene and verified absorption by isolation of the drug from the urine. These were the first cases reported in this country. In other parts of the world, however, cases have been reported both in children[7–10] and in adults.[8, 10, 11] Poisoning was due to the use of naphthalene in the treatment of typhoid fever[8] or oxyuriasis,[11] accidental ingestion,[7–9] or industrial poisoning —usually by inhalation of the vapors or through the skin.[10] Poisoning from naphthalene has resulted from inhalation of the vapor by exposure of individuals during sleep to bed

* A discussion of methemalbumin can be found in Wintrobe's *Clinical Hematology*.[4]

clothing that had been dusted with naphthalene powder, and from its application to open wounds.[10] Naphthalene also may cause cutaneous manifestations.[12, 13]

The infant presented here was born after a normal pregnancy and an uncomplicated delivery in a hospital and was well until she went home at the age of three days. At that time the diapers were taken out of storage; they smelled strongly of mothballs. The baby's skin was rubbed down daily with oil. Although naphthalene is not appreciably soluble in water, it is very soluble in oil. Within two days, jaundice and cyanosis were noticed. These symptoms persisted along with a fall in hemoglobin and increasing hemoglobinuria, even though no further exposure to contaminated diapers occurred. It is probable that the body would continue to absorb naphthalene already in the skin. Unfortunately, the small sample of urine obtained from this infant at post mortem was used up in routine and spectroscopic studies before naphthalene poisoning was suspected; hence, urinalysis for naphthalene could not be done.

Summary

A case of acute hemolytic anemia in a newborn infant apparently due to naphthalene poisoning is reported. It is thought that absorption through the oiled skin occurred following repeated exposure to diapers which had been stored in naphthalene mothballs and moth crystals.

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Spanish Abstract

Anemia Hemolítica Aguda Producida Por Naftalina; Reporte de un Caso en un Recién Nacido

Se reporta un caso de anemia hemolitica aguda en un reción nacido aparentemente causada por intoxicación con naftalina. Se indica que la absorción de la naftatlina ocurre a través de la piel grasosa, cuando esta está expuesta a contactos repetidos con pañales que han estado almacenados en sitios conteniendo bolas o cristales de naftalina.

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ENDOCARDIAL FIBROELASTOSIS

Report of Two Cases

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DURING the past 10 years 205 autopsies were conducted at the New Britain General Hospital on infants under 2 years of age. This experience disclosed two instances of deaths resulting from congenital fibroelastosis of the endocardium. Because of the relatively few reports of this disease that have been found in the literature, it appeared desirable to present here a summary of the clinical and anatomic observations on these two cases.

CASE REPORTS

Case 1.* This 7 mo. old male infant was born at the New Britain General Hospital. It was the first pregnancy of a 31 yr. old mother, whose prenatal course was characterized by moderate nausea and vomiting, but no febrile or exanthematous disease. The sole abnormality noted at birth was an area of skin hemorrhage over the right sternocleidomastoid muscle. The child was bottle-fed from birth. Because of watery stools alternating with pasty yellow stools, his formula was changed several times. His cry was normal until the age of 3 mo., when it became hoarse and whining. His general development was retarded, particularly in motor activity. Because of the repeated episodes of diarrhea the child was referred to another hospital, where detailed studies were conducted. Electrocardiograms taken at this time showed a sinus tachycardia. Skull plates and electroencephalograms were noncontributory. He was discharged from that hospital at 5 mo. of age with a final diagnosis of mental retardation, cause unknown; congenital heart disease, incompletely diagnosed; diarrhea, cause unknown; question of Mitchell-Rubin's disease. The child returned home where he did well until about 3 days prior to admission to the New Britain General Hospital at 6 mo. of age. At that time dyspnea accompanied a slight nonproductive cough. On the day of admission the infant vomited several times. After each episode of vomiting labored breathing and a dark dusky skin color were noted. On admission the child had marked inspiratory thoracic retraction with accompanying crowing respirations. The anterior fontanel was under increased tension. Respiratory rate was 60. Tubular breath sounds were heard over the left apex posteriorly. Cardiac examination disclosed a heart which was not enlarged. Heart sounds were normal. A blowing apical nontransmitted systolic murmur was audible over the precordium. There was no diastolic murmur. The apical and peripheral pulse rates were both 130/min. The sole positive finding on abdominal examination was a liver enlarged to 3 fingerbreadths below the costal margin in the right midclavicular line. A moderate rigidity of the extremities was noted. The admission RBC count and Hgb. were within normal limits. WBC count was 13.6 thousand/cmm. with 69% polymorphonuclears and 5% nonsegmented forms. The admission chest plate showed consolidation of the entire left lung and a portion of the right lung. This was interpreted as viral in origin. The impression on admission was aspiration pneumonitis, question of virus pneumonitis and cardiac decompensation.

Shortly after entering the hospital the patient developed severe and extreme pulmonary edema, for which he was treated with oxygen, intravenous aminophylline, glucose, digitalis and morphine. He also received large doses of aureomycin, chloramphenicol, penicillin and triple sulfonamides, without effect on the pulmonary findings, clinical or radiologic. ECGs were suggestive of a nodal rhythm, and revealed a sinus tachycardia with ST segments depressed in Lead 3, and a short PR interval.

Grunting respirations continued throughout the patient's hospital course, accompanied by gross

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* The authors are grateful to Dr. Roswell D. Johnson for permission to report this case.

hemoptysis and melena. Because of a RBC fall to 1.8 million/cmm. with a Hgb. 6.2 gm./100 cc., a transfusion of whole blood was started in a scalp vein on the 10th hospital day, with full appreciation of the hazard of acute heart failure. After 20 cc. of blood had been injected slowly, the child became restless, dislodging the needle from the vein. Death occurred some 15 min. after the needle was withdrawn. The autopsy permit excluded examination of the cranial contents.

Gross Autopsy Findings: The body was that of a moderately well developed and fairly well nourished, white male infant weighing an estimated 5.4 kg. and measuring 60.0 cm. in length. External examination was negative. There was an absence of cyanosis of the mucous membranes and nailbeds. The heart, which weighed 57 gm., was opened in the usual manner revealing a right atrium of normal size and thickness. The endocardial surface of the right auricle was moderately thickened

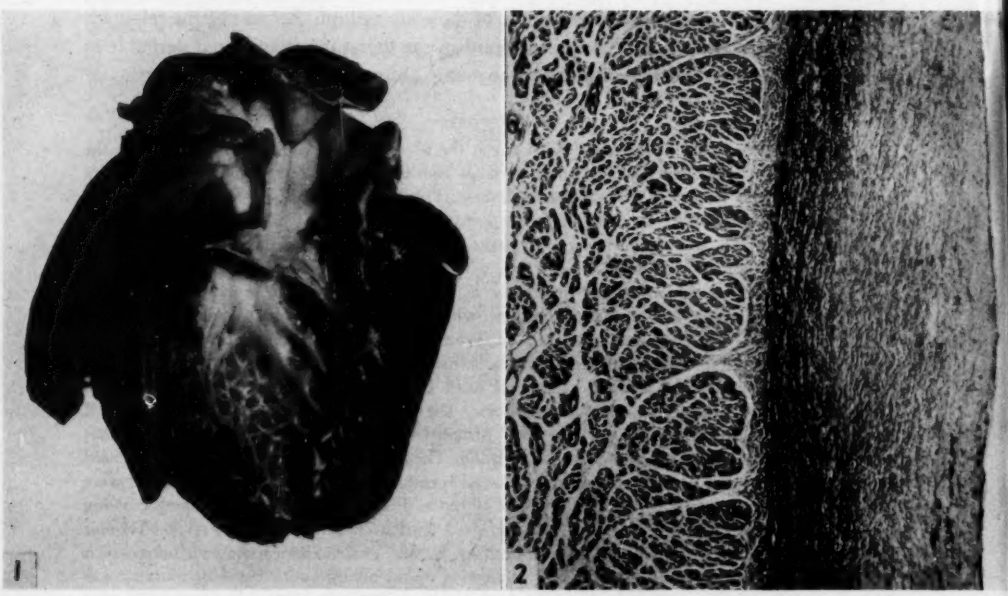

FIG. 1. Gross photograph of heart, Case 1, showing thickened endocardium of left auricle and ventricle, with dilatation of left ventricle, and flattening of columnae carneae and papillary muscle. (All photographs were prepared by Mr. Howard J. Reynolds.)

FIG. 2. Thickened endocardium of left ventricle, Case 1. Verhoeff elastic tissue stain, counterstained with crystal violet and Rose Bengal. × 43.

by milky-white bands of fibrous tissue. The right auricular appendage was devoid of antemortem thrombus. The chordae were thin, velamentous, and not fused. The papillary muscles of the right ventricle were covered by the same type of thickened milky-white endocardium noted on the atrial surface. The pulmonary artery was dissected to its point of bifurcation into the pulmonic parenchyma where no anomalies could be discerned. At no point was there any constriction or hypoplasia of the pulmonic vascular tree. The endocardial surface of the left atrium and portions of the endothelial surface of the pulmonary veins were markedly thickened. The endocardium of the left auricular appendage in places measured 0.15 cm. in thickness. The papillary muscles in the left ventricle were hypertrophied and covered by the same type of thickened endocardium as that observed in the left atrium. The endocardium throughout the left ventricle was thickened and milky-white (Fig. 1). The base of the papillary muscles and all of the columnae carneae were flattened and covered by thickened, dense, white endocardium. All the valves were without abnormality. The aorta was not remarkable.

Both the ductus arteriosus and the foramen ovale were closed. Approximately 200 cc. of clear, amber, watery fluid were found in each of the hemithoraces, and about 25 cc. of similar fluid had accumulated in the pericardial cavity. The abdominal cavity contained 200 cc. of similar fluid. Numerous petechial hemorrhages were present on the visceral pleural surfaces of both lungs. The bronchi contained a slight amount of tan mucoid material. Cross section of the lungs revealed increased fibrosis of the parenchyma. Bloody mucoid fluid was found in the esophagus and in the stomach. Bloody intestinal content was noted in varying amounts throughout the entire intestinal tract, the mucosal surface of which appeared uniformly pale and nonulcerated. The liver was somewhat paler than normal.

Microscopic Findings: The thickened endocardium of the left atrium and ventricle was due to a

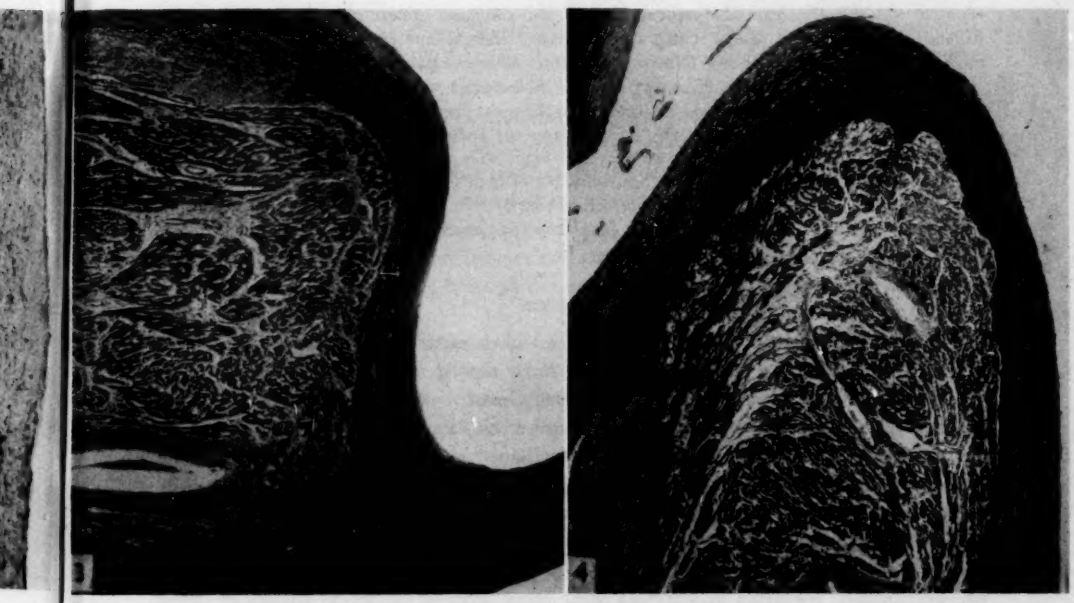

FIG. 3. Thickened endocardium of left ventricle and base of mitral valve, Case 1. Verhoeff elastic tissue stain, counterstained with crystal violet and Rose Bengal. × 43.

FIG. 4. Thickened endocardium of left ventricle, Case 2. Verhoeff elastic tissue stain, counterstained with Van Gieson stain. × 43.

hyperplasia of the fibrous and elastic tissue as demonstrated by the differential staining technics of Masson and Verhoeff. Comparison with a nondiseased heart of an infant of approximately the same age showed that in places the endocardium was approximately 15 times as thick as that found in the normal heart. That the fibrous and elastic tissue was not laid down in concentric layers was easily shown; rather was the picture that of an intermingling of fibrous connective tissue and elastic tissue within the endocardium which dipped down and around the columnae carneae and papillary muscles into the interdigitations of the myocardium. Fibrosis or hyperplasia of the elastic tissue within the myocardium was not demonstrated, nor was there any apparent infiltration of the myocardium by this hyperplastic fibroelastic tissue (Figs. 2 and 3). Pulmonary congestion and fibrous thickening of the alveolar walls were present. Scattered throughout the pulmonary parenchyma and in the bronchiolar lumina were many large mononuclear hemosiderin-laden macrophages. The microscopic findings in the other organs were noncontributory.

Case 2. This female infant was born prematurely after artificial induction of labor. She was

admitted to the New Britain General Hospital when 3½ mo. of age with a history of grunting respirations and vomiting of several weeks' duration. On admission the child was poorly developed and in no acute distress. The weight was 3.5 kg. Rapid and labored respirations were associated with grunting and sternal retraction. The admission temperature was 37.2°C. Twelve hours after admission the infant developed an acute respiratory difficulty and died.

Gross Autopsy Findings: Fluid in varying amounts was found in all the body cavities. The lungs were atelectatic, and the heart within its pericardial sac was markedly enlarged. A patchy diffuse milky-white, thickened endocardium was seen in the entire right auricle with the exception of the auricular appendage where the endocardium was of normal thickness. The base of all the cusps of the tricuspid valve was enveloped by the thickened endocardium. The chordae tendineae were inserted normally. Fibrosis and opaque thickening of the endocardial surface of the entire right ventricle was also apparent. The papillary muscles and columnae carneae of the left ventricle were flattened and covered by opaque milky-white thickened endocardium. Both the foramen ovale and the ductus arteriosus were closed. Extensive congestion of all the parenchymatous organs was noted.

Microscopic Findings: The microscopic changes in the heart were essentially the same as those described in Case 1. The thickening of the endocardium was the result of a marked increase in the fibrous and elastic tissue elements (Fig. 4). In places the endocardium was estimated to be about 30 times the normal thickness. Although the elastic fibers were most numerous in the basal portions of the endocardium, there was a distinct intermingling of both the fibrous and elastic tissue elements in the thickened endocardium. Inflammatory cells were not seen and there was no evidence of myocardial fibrosis, either diffuse or focal. The lungs and liver showed marked chronic passive congestion. The remaining organs were not remarkable.

Discussion

The cardiac abnormality occurring in infants, and characterized by a peculiar thickening of the endocardium, has been the subject of many reports. This lesion has been termed "fetal endocarditis" by many workers.[1–6] In 1941 Gross[7] reviewed the literature and added one case of his own. He emphasized the absence in his case of any evidence of inflammation, and stated that the abnormality "is best explained as simple hyperplasia of the endocardial fibroelastic tissue." Pototschnig[8] was the first to advance this hypothesis.

The two cases here presented, together with 11 others reported by various observers,[7, 9–15] have been critically reviewed in an attempt to evaluate the pathogenesis of this disease. Particular attention has been given to several variables including maternal history, age distribution, associated cardiac and other abnormalities, the site of the lesion in the different heart chambers, the presence or absence of cardiac hypertrophy, and the histologic evidence of inflammatory disease of the myocardium.

Five of the 13 cases gave a history of maternal infection during the pregnancy which resulted in the affected infant. One of these mothers had infectious mononucleosis during the first trimester, another suffered from an attack of an upper respiratory infection during the first and last trimesters, a third had an episode of rhinitis at an unstated time during her pregnancy, a fourth had a tooth extracted during the first trimester and a Bartholin gland abscess during the second trimester, and the fifth mother suffered from diarrhea, vomiting and dizziness, diagnosed as la grippe, during the first month of her pregnancy. All these maternal illnesses were inflammatory in nature, but the etiology of the illness in one other mother is questionable. She had vaginal bleeding during the first trimester. Thus, of the 13 cases reviewed, six gave a history of maternal disease during the prenatal period, and 5 of these 6 illnesses were of an inflammatory or infectious type. The absence of positive statements of uncomplicated pregnancies in the remaining seven cases is of questionable significance. There was no correlation between the parity of the mother or

the type of delivery, and the development of endocardial fibroelastosis in the infant. Information regarding blood groups, Rh types and transfusions was not available.

The age group in which this morphologic alteration was found extended from a premature newborn infant to a child 5 years of age. Twelve of the 13 cases were less than 27 months old, and 9 were under 5 months of age. It is of significance that the fibroelastic thickening of the endocardium was found in a premature infant, for this observation indicates that whatever the pathogenesis may be, it may be operative in early fetal life. All the patients died in cardiac failure as the terminal event.

Seven of the 13 cases presented associated cardiovascular anomalies other than dilatation or hypertrophy of the cardiac chambers. In 5 of these 7, the other abnormalities were located in the great vessels of the heart, and the remaining two presented developmental anomalies of the heart chambers. Cardiac hypertrophy was observed in all but one of the 13 cases, as determined by comparison with the normal heart weights of infants tabulated by Coppoletta and Wolbach.[16] None of the case reports mentioned the presence of congenital anomalies other than those in the cardiovascular system.

Complete data were not available in all cases, but positive statements of cardiac dilatation or hypertrophy appeared in over half the case reports. Fibroelastic thickening of the endocardium was observed in the left ventricle of all 13 hearts. Ten showed the change in both the left ventricle and left auricle; two showed involvement of the endocardium of the left ventricle only, and one heart had endocardial thickening in both ventricles and in the right auricle.

With the exception of the endocardial lesion, none of the usual evidences of an inflammatory reaction were present in any of these hearts. Cellular infiltrates, vascular proliferation, deposition of fibrous tissue, edema and necrosis all were absent on histologic examination. Even the thickened endocardium occurred in an orderly arrangement of fibroelastic elements which did not suggest that inflammation was the basic lesion. The thickened endocardium occurred diffusely throughout the heart chamber, and not focally as is so often seen after healing of a myocardial infarct. On both gross and microscopic study there was no specific change which could be cited as evidence of an inflammatory anlage in the production of this lesion.

Several hypotheses have been advanced in an attempt to solve the problem of the etiology of endocardial fibroelastosis. The designation "fetal endocarditis" suggests that the lesion is the end result of an in utero inflammatory process involving the endocardium. But, as has been seen, none of the changes usually accompanying an inflammatory process were evident histologically. Even in the youngest infant, prematurely born, there were no active inflammatory components evident. It is conceivable that the thickened endocardium might possibly be the end-result of an inflammatory process, but if this be so, one would anticipate finding definite evidence of inflammation in an occasional case. Such evidence was consistently absent.

Pototschnig[8] in 1918 suggested that the lesion is noninflammatory in origin, and two theories of pathogenesis have since been advanced on this basis. Boger[17] postulated an overstretching of cardiac chambers with dilatation and resultant endocardial fibrosis. This result has not been observed in the hypertensive heart, where the endocardial surface of the dilated chambers is usually devoid of thickening, if unassociated with myocardial ischemia. Furthermore, if this theory were true, one would still have to explain the reason for the postulated overstretching of the heart chambers. The fibrosis of endocardium which

results from a healed infarct is ordinarily accompanied by fibrosis of the myocardium, a change which was not evident in the hearts showing endocardial fibroelastosis.

Another hypothesis appears at this stage in our knowledge to be more credible. This suggests that the changes described are due to a developmental abnormality, the exact nature of which is as yet unknown. It should be remembered that associated cardiovascular defects were noted in 7 of the 13 cases reviewed. Weinberg and Himelfarb's report[11] of the disease process in two siblings lends weight to the theory of developmental abnormality, because it is well known that the probability of occurrence of a congenital developmental abnormality is increased if previous pregnancies have resulted in congenital defects. Five of the mothers of these 13 infants had a known infectious or inflammatory illness during pregnancy, and it is entirely likely that a more careful review might have elicited a history of similar illnesses in some of the other mothers. Infectious, dietary and immunologic disorders are known to be responsible for a variety of congenital malformations in experimental animals and, by analogy, might also initiate developmental abnormalities in man. In this connection, as pointed out by Katzenstein,[15] the influence of rubella during pregnancy on the incidence of abnormalities in the offspring has been emphasized by Gregg[18] and confirmed by many others. A similar mechanism might be operative in the production of endocardial fibroelastosis of infants.

In a consideration of the mechanism of production of developmental abnormalities, it is important to differentiate between two different processes. The first is a true aberration in the germ plasm, an alteration in the genetic constitution, which produces an abnormality in the developing fetus. The second is actually the result of an external, i.e., environmental, influence on the fetus, which has been developing normally until the time of exposure to this environmental change. Such an environmental factor may well be the result of maternal disease of an infectious, nutritional, hormonal or other type. In reviewing the pathogenesis of endocardial fibroelastosis, it is not possible at this time to differentiate between these two mechanisms.

Summary

Eleven cases of fibroelastosis of the endocardium are reviewed and two new cases reported.

The microscopic evidence of hyperplasia of the fibrous and elastic tissue elements of the endocardium in the two new cases reported parallels the findings in the previously reported cases.

The pathogenesis of this lesion is at present not clear, although it is probable that the explanation lies in a developmental aberration in the fetus.

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SPANISH ABSTRACT

Fibroelastosis Endocárdica; Reporte de Dos Casos

Los autores hacen una revisión de once casos de fibroelastosis endocárdica y reportan dos casos adicionales. Los cambios histológicos observados en el endocardio (hiperplasia del tejido fibroso y elástico) en los dos nuevos casos fueron similares a las alteraciones pathológicas previamente descritas en casos de fibroelastosis endocárdica. La patogenesis de estas lesiones es obscura, pero los autores sugieren como explicación posible, la ocurrencia de una aberración en el desarrollo del feto, secundaria a enfermedades maternas durante el período de gestación.

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RENAL CARBONIC ANHYDRASE IN PREMATURE AND MATURE INFANTS

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RENAL carbonic anhydrase has been shown by Höber[1] to be of importance in the acidification of urine. Pitts[2] believes that the process of acidification is an enzyme-accelerated exchange of sodium and hydrogen ions in the distal tubule. In this connection the work of Beckman and co-workers[3] on the acidosis of sulfanilamide poisoning is of interest. Although their work was completed before the role of carbonic anhydrase was generally appreciated, they concluded that the type of acidosis produced was primarily renal in origin. A deficiency in the conservation of sodium appears from their data to have been present. Sulfanilamide is known to inhibit carbonic anhydrase, though the levels in the blood ordinarily reached are far short of those required to inhibit the enzyme so long as it is contained within the intact red cell (Anderson and Thompson[4]). Therefore it is likely that the acidosis of sulfanilamide poisoning results from inhibition of the renal carbonic anhydrase. The work of Stevenson[5] demonstrates that premature infants have a low level of carbonic anhydrase activity in the blood. The question is therefore raised as to the level of the enzyme in the kidneys of premature infants. If the level were low, premature infants might represent a physiologic example of a situation analogous to that found in sulfanilamide poisoning. Although it is known that premature infants can produce an acid urine, with a pH as low as 4.7,[6] it is possible that some of them under stress such as that produced by the administration of ammonium chloride may, as reported by Gordon, McNamara and Benjamin,[6] display poor sodium conservation.

Studies of the level of carbonic anhydrase activity in the kidneys of premature infants as compared with mature infants and adults are therefore in order and are presented in this communication. From this data, it appears that the kidney carbonic anhydrase of premature infants is not greatly if at all lower than that in full term infants and adults. The situation is very different from that obtaining for the enzyme in the blood, where the activity in premature infants is only some 10% of that in the older subjects, in most instances.

METHODS

Kidneys were taken from subjects who had died of nonrenal causes. Carbonic anhydrase is a rather stable enzyme and no deterioration was noted in postmortem specimens kept under refrigeration for several days. Portions of the renal cortex and medulla were separated by gross dissection, since the tubules are contained within the cortex. The work of Höber[1] indicates that the site of the renal carbonic anhydrase is the tubules. Two hundred fifty mg. of material (cortex or medulla) were ground with sand for 5 min. with 1.75 ml. of M/15 Na_2HPO_4. The suspension thus obtained was centrifuged and 0.8 ml. of supernatant liquid diluted to 10 ml. One tenth ml. of the final solution was used in the test.

Carbonic anhydrase activity was measured by the method of Meldrum and Roughton.[7] Activity of

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the enzyme is expressed in the arbitrary E units described by these authors. In the data, the activity reported is that contributed by 1 mg. of kidney tissue, wet weight.

It was not possible to prepare specimens free from blood. As a check on each other, 2 different methods were used to allow for the enzyme activity contributed by the contaminating blood. The first method depends upon the fact (Höber[1]) that renal carbonic anhydrase is in the distal tubules, which lie in the cortex. The difference between the activity in the cortex and in the medulla was taken to be the activity of the renal cortical carbonic anhydrase. For the purpose of the calculation the enzyme activity of the blood unavoidably entering the test solution was disregarded, since it was found that the degree of contamination by blood was very nearly the same in the 2 portions of the organ. The second method of discounting the contaminating blood was to measure the hemoglobin in the final test solution by the method of Ashby.[8] The amount of enzyme activity likely to have been introduced by the blood was then corrected for the weight of the subject, as indicated by the data on the blood carbonic anhydrase in infants of different weights (chart 1). Since postmortem specimens were being used, direct measurement of the blood carbonic anhydrase was not feasible.

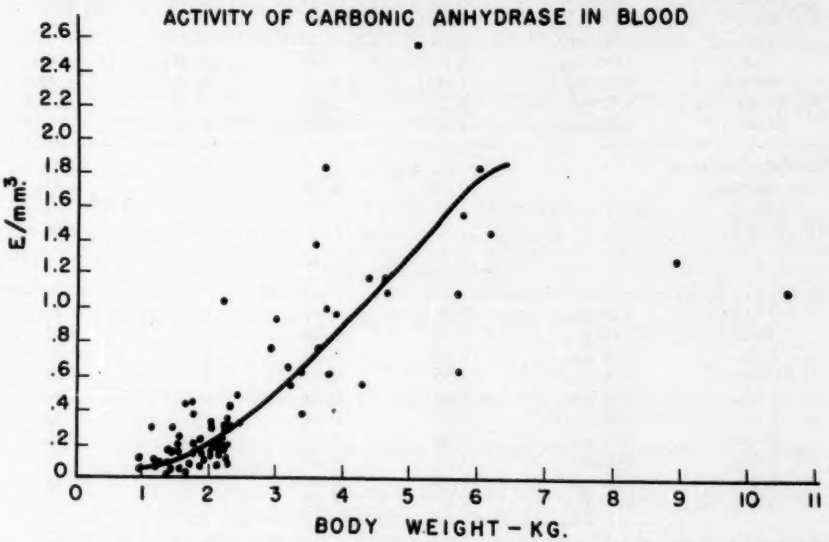

CHART 1. Level of carbonic anhydrase activity in blood of infants of varying weights.

RESULTS

The results appear in table 1. There is a large variation in the values which must be ascribed to error. The error of measurement is ±18%; that is, the coefficient of variation in 20 successive measurements of renal cortical carbonic anhydrase taken from the same kidney was 18%. An important source of error is the contaminating blood, the method of allowing for which has been described. The difficulty with contaminating blood was greater in the case of adult kidneys, where 45% of the total cortical activity was the result of the presence of blood. In the premature infant kidneys only about 18% of the total uncorrected cortical enzyme activity was the result of the inadvertent admixture of blood. Other sources of error were found to be variations in wetness of specimens and failure completely to separate cortex from medulla.

The average values given in the table do not show any real difference between premature infants and mature infants or adults. The variations from subject to subject are

TABLE 1

ENZYME ACTIVITY UNITS (E)/MG. KIDNEY SUBSTANCE

Age	Body wt.	Renal cortex	Renal medulla	Excess in cortex Col. 1–Col. 2	Cortical enzyme, corrected for contaminating blood
		1.	2.	3.	4.
Premature Infants					
9 hr.	650 gm.	0.50	0.23	0.27	0.49
2 days	670 gm.	0.56	0.09	0.47	0.54
39 hr.	680 gm.	0.32	0.14	0.18	0.27
8 hr.	880 gm.	0.37	0.07	0.30	0.32
8 hr.	950 gm.	0.54	0.19	0.35	
2 hr.	1330 gm.	0.50	0.43	0.07	0.49
Stillborn	1540 gm.	1.00	0.61	0.39	0.89
9 hr.	1570 gm.	0.57	0.25	0.32	0.56
14 hr.	1850 gm.	1.18	0.55	0.63	
Standard Deviation				0.15	0.19
Mean (average)		0.62	0.28	0.33	0.51
S.D. of mean				0.05	0.07
Mature Infants					
3 days	2720 gm.	0.67	0.33	0.34	0.63
3 wk.	3000 gm.	1.12	0.68	0.44	1.07
3 wk.	3100 gm.	1.22	0.50	0.72	0.88
Stillborn	3200 gm.	0.93	0.83	0.10	0.33
6 wk.	3300 gm.	0.61	0.29	0.32	0.29
1 hr.	3400 gm.	0.87	0.74	0.13	0.53
7 min.	3600 gm.	0.96	0.33	0.63	0.88
2 mo.	3850 gm.	0.72	0.79	−0.07	0.64
5 mo.	4420 gm.	1.25	0.86	0.39	1.24
6 mo.	5800 gm.	0.83	0.52	0.31	0.67
Standard Deviation				0.23	0.29
Mean (average)		0.92	0.59	0.33	0.72
S.D. of mean				0.07	0.09
Adults					
36 yr.		1.11	0.50	0.61	0.51
37 yr.		1.04	0.42	0.61	0.84
40 yr.		1.30	0.56	0.74	1.08
41 yr.		1.32	0.58	0.74	1.28
43 yr.		0.73	0.38	0.35	0.53
45 yr.		0.84	0.54	0.30	0.64
48 yr.		1.03	0.59	0.44	0.03
53 yr.		1.03	0.45	0.58	0.63
54 yr.		0.92	0.38	0.54	0.32
Standard Deviation				0.16	0.35
Mean (average)		1.04	0.49	0.55	0.65
S.D. of mean				0.05	0.12

too large to permit the statement that no increase at all takes place in the enzyme with increasing maturation of the subject, but if there is any such increase, it must be relatively slight. Kidney carbonic anhydrase is very different from that of the blood with respect to increase in activity with increasing age of the infant. The blood of 10 older maturely born infants with an average body weight of 6500 gm. had a blood carbonic anhydrase activity of 1.49 E/cmm., with a Standard Deviation of 0.41. Fourteen premature babies with an average body weight of 1600 gm. had 0.15 E/cmm. blood, with a Standard Deviation of 0.10. Thus the mature infants displayed 10 times as much blood carbonic anhydrase activity as did the premature infants. The variations in blood enzyme from patient to patient were found to be as large as those for the kidney carbonic anhydrase, and yet the mean difference between the values for the mature and the premature infants was nearly 11 times its Standard Deviation, indicating a very high degree of reliability. In contrast, the kidney enzyme displays no clear evidence of a change with maturation of the subject. Chart 1 displays the trend in blood enzyme levels among infants of different weights.

These measurements do not indicate whether the enzyme shown to be present in the kidneys of premature infants actually aids in the acidification of urine.

Summary

The carbonic anhydrase activity in the kidneys of premature infants was studied because it was thought that if the renal enzyme is as deficient as that in the blood, inefficiency in acidification of urine might result. In contrast with the blood, postmortem specimens of kidneys of premature infants were found to exhibit carbonic anhydrase activity similar to that found in the case of kidneys from older infants and adults.

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Spanish Abstract

La Anhidrasa Carbonica Renal en Prematuros y Niños a Termino

La actividad de la anhidrasa carbonica en los riñones de prematuros fué estudiada con la idea de comprobar si ésta enzima renal es tan deficiente como la anhidrasa sanguinea, cosa que pudiera resultar en una deficiencia en la acidificacion de la orina. En contraste con la anhidrasa carbonica sanguinea el analisis post-mortem de los riñones de prematuros demostró una actividad de anhidrasa carbonica similar a la encontrada en los riñones de niños a termino y personas adultas.

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TISSUE CHANGES IN THE NEPHROTIC SYNDROME: DEMONSTRATION OF POTASSIUM DEPLETION

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THE object of this investigation was to ascertain whether tissues such as muscle, kidney and liver taken from patients showing the nephrotic syndrome exhibit chemical alterations beyond those attributable merely to accumulation of edema fluid.

Previous studies[1] have shown that this syndrome is usually associated with reduction in concentration of plasma sodium (hyponatremia) and decreased concentration of bicarbonate (acidosis). Subsequent analyses showed in many instances subnormal plasma potassium concentration. The urine of these subjects is low in both sodium and chloride but the potassium concentration is greatly increased (hyperkaluria). Since these abnormalities persist along with the anasarca for weeks and months, it seemed reasonable to suspect that chemical alterations within the cells of the body might also prevail.[1]

The administration of potassium acetate and sodium lactate, which are converted in the body to their bicarbonates, restored the extracellular concentrations to normal and diuresis occurred in a number of instances.[1, 2] Although exact data from complete balance studies is lacking, intracellular replacement of potassium was suggested by comparison of the oral intake and urine output.

In the course of these therapeutic trials in 43 children, certain complications, including hypokalemia, arose in five instances. After several months of persistent anasarca and albuminuria, including one or more months of hospitalization, these children died.* An additional child (6W), with chronic nephritis and anasarca, died of an intercurrent infection. Samples of muscle, liver and kidney were obtained for direct chemical analysis when the autopsy was performed. The present report describes the results of these measurements. Similar studies have been performed on tissues of rats with the nephrotic syndrome produced by Heymann[3] by administration of anti-rat kidney serum. These data will be reported elsewhere.

To ascertain the effects of postmortem changes, tissues were also obtained from children who died from other causes not believed to be associated with significant electrolyte or water disturbances.† A biopsy of a normal human rectus muscle is also included.

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Preliminary data were presented by title before the Society for Pediatric Research in Atlantic City, May 1949; this paper was read at the National Meeting of the American Federation for Clinical Research, May 2, 1950.

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* The renal lesions were diagnosed as nephrosis in patients M and D, as subacute glomerular nephritis in R, in F the decision lay between these 2 diagnoses and T and W were nephritis. Hyperazotemia was not present in any patient.

† This material was made available by Dr. Dorothy Andersen of the Babies Hospital.

The methods used were as follows:

Sizeable pieces of various muscles, usually 2 x 4 cm. of rectus abdominis, and of other organs were removed from the refrigerated bodies from 1 to 6 hr. after death. The samples were trimmed free of superficial fat and connective tissue and weighed. They were then dried at 105°C. to constant weight. Small samples were taken for digestion and direct nitrogen analysis by Kjeldahl. The major portion was extracted with dilute nitric acid, as described by Lowry and Hastings,[4] and sodium, potassium, chloride and phosphate determinations were performed on aliquots of the same sample. Sodium and potassium were determined with an internal standard flame photometer[5] built in the present authors' laboratory. Details of these methods and the accuracy obtainable has been described previously.[6] Chemical methods were used for chloride*[7] and total phosphate.[8]

Results

The results of all the tissue analyses are shown in tables 1A and 2. All values are given in terms of the dry weight of the cell solids. Thus, the simple addition of extracellular edema should have negligible effects on the concentration of cell components per unit dry weight.

The values obtained for the control analyses agree with the values found in the older literature,[9] and with recent data derived from biopsy at operation.[10, 11] There is, of course, no apparent reason why the potassium and phosphate content of muscle tissues should change after death.

The muscles from the nephrotic patients are markedly different from the controls. The content of water, sodium and chloride are greatly increased. In contrast, potassium is considerably decreased, more in some than in others. Phosphate is only slightly altered. These changes were found in all the individual muscles analyzed; the variations are in degree but not in direction. Some remaining duplicate samples were defatted and similar values resulted.

The liver analyses in table 2 show but small deviations from normal. Despite the marked ascites present for a long time in all patients, the water content of these livers are usually below normal.

The kidneys present a different pattern. Like the muscles, their contents of water, sodium and chloride are considerably increased; unlike the muscles, their potassium content is increased. The antecedent hyperkaluria may be an important factor here.

Discussion

It is not easy to evaluate the significance of these data. To avoid any agonal or post-mortem changes, analyses of biopsy specimens would be preferable. Until such data are available the present values must be interpreted cautiously. However, the "control" post-mortem values and other similar samples do not deviate greatly from those on freshly obtained samples. Furthermore, these patients with nephropathy all died suddenly or unexpectedly so that protracted agonal changes can be excluded.

Increases in tissue water, sodium and chloride indicate edema usually interpreted as an expansion in the volume of interstitial fluid surrounding the cells. Inasmuch as all these patients had protracted anasarca, this would be the simplest explanation for the increases in tissue water, sodium and chloride. This explanation, however, does not account for the reduction in muscle potassium.

Decreases in the potassium contents of skeletal muscle have been produced experi-

* Ammonium sulfamate must be added to the dilute HNO_3 to destroy traces of HNO_2 prior to iodimetry.

TABLE 1A

COMPARATIVE TISSUE ANALYSES IN NEPHROTIC SYNDROME

Patient	Sample number	Muscle H_2O	H_2O	Na	Cl	(PO_4)	K	N	Na+K
		(gm./100 gm. wet wt.)	(gm./100 gm. dry wt.)	(mEq./100 gm. tissue solids)				(gm./100 gm. tissue solids)	(mEq./l. H_2O)
1M*	1	84.2	532	67.4	33.8	—	14.5	14.7	154
	2	84.8	556	75.0	36.2	35.0	13.7	—	160
2T	3	85	566	72.6	36.0	31.0	20.0	—	163
	4	84	525	50.5	26.0	37.4	25.5	—	144
*	5	83	490	45.4	22.0	—	30.2	14.2	154
3F	6	84.5	545	72.4	36.4	26.1	26.0	—	181
	7	83.5	506	62.1	34.8	24.2	23.3	—	169
4R	8	83	488	46.1	36.6	34.0	32.8	—	162
5D	9	81.6	444	32.2	18.2	29.6	33.7	14.2	148
	10	81.6	444	31.3	—	26.3	35.5	14.8	150
	11	80.9	423	31.3	22.1	32.3	34.5	13.2	156
	12	81.8	450	29.6	—	32.4	38.5	13.5	152
6W	13	83.1	492	34.8	21.0	26.8	35.4	14.9	143
	14	84	525	27.3	15.3	27.6	35.9	14.8	120
(thigh)*	15	83.4	640	55.5	34.1	—	25.9	14.4	127
Average		83.2	520	48.9	28.7	30.2	28.4	14.2	149
S.D.		1.2	66.9	17.9	7.2	3.41	7.16	0.78	
Control 1		79.4	385	13.7	11.4	31.6	42.7	—	146
		81.5	440	15.3	12.6	31.4	43.0	—	132
		81.4	437	17.3	13.3	31.7	41.3	—	134
Control 2		79	376	16.7	9.97	—	47.3	—	170
		78	354	15.1	9.5	—	45.2	—	170
Biopsy of normal*		77	320	12.0	10.3	—	43.0	15.5	172
Average		79.3	385	14.9	11.2	31.6	43.8	15.5	
S.D.		1.65	42.8	1.78	1.39	—	1.95	—	

*Analyses are per 100 gm. fat free dry weight.

TABLE 1B

EXPERIMENTAL POTASSIUM DEPLETION OF MUSCLE

*Control[11] (rat)	76.4	324	7.6	4.9	33.5	46.2	—	166
K deprived	76.4	324	22.8	5.4	32.9	27.2	—	155
*Control[13] (dog)	76.8	331	14.5	10.0	—	34.6	15.0	148
Doca 1 mo.	79.2	381	29.7	14.5	—	22.7	14.8	138
*Control[14] (rat)	77.2	340	10.0	7.1	32.4	48.9	15.3	173
Doca-low K	76.5	326	19.8	5.5	26.5	34.0	15.0	165
Alkalosis	77.0	337	15.2	5.0	31.7	38.2	14.7	158
†Tourniquet Injury[6] (mice)	82.0	456	70.6	51.2	—	15.1	—	188

* Data taken from references cited.
† Analyses performed in this laboratory.

TABLE 2

COMPARATIVE ANALYSES OF ORGANS IN NEPHROTIC SYNDROME

Patient	H_2O		Na	Cl	(PO_4)	K	N	Na+K
	(gm./100 gm. wet wt.)	(gm./100 gm. dry wt.)	(mEq./100 gm. dry wt.)				(gm./100 gm. dry wt.)	(mEq./l. H_2O)
				Liver				
1M	71	244	24.4	14.8	33.2	30.4	—	225
2T	73	270	18.4	11.2	33.2	25.4	—	162
	74	284	22.3	13.2	35.8	24.6	—	165
3F	79.3	382	31.0	20.3	44.2	34.4	—	171
*	79.3	404	39.4	26.2	—	36.6	—	188
5D	75.8	313	37.2	18.6	32.0	19.0	8.6	179
6W	70.9	243	13.5	12.0	23.5	22.7	—	149
	72.5	264	16.9	—	26.4	23.1	—	151
Average	74.5	300.5	25.4	16.6	32.6	27.0	—	174
S.D.	3.2	58.0	8.9	5.0	6.1	5.7	—	
Control 1	77.1	337	19.6	11.5	35.6	28.4	—	142
Control 2	76	316	27.6	17.9	—	23.8	—	
Average	76.5	327	23.6	14.7	35.6	26.1	—	152
				Kidney				
1M	84	525	64.4	38.0	50.5	27.8	—	176
2T	86	614	64.9	33.9	52.7	36.5	—	165
	85	566	66.0	34.3	—	40.7	—	189
3F	84.8	558	51.4	32.4	—	27.1	—	138
*	84.8	660	62.5	38.8	—	35.9	—	149
5D	84.3	536	69.1	30.6	45.0	26.6	12.0	179
	82.4	467	61.1	—	36.0	20.8	9.6	176
6W	86.7	651	63.9	35.1	—	37.6	—	156
	86.9	663	64.5	—	42.1	38.6	13.3	155
Average	84.9	582	63.1	34.7	45.3	32.4	11.6	164
S.D.	4.4	215	4.6	2.7	6.0	6.5	—	
Control 2	76	316	27.6	17.9	—	23.8	—	163

*Analyses are per 100 gm. fat free solids.

mentally after prolonged potassium deprivation by Heppel[12] and by Conway;[13] after protracted administration of desoxycorticosterone by Ferrebee et al.;[14] and after alkalosis by Darrow.[15] In all these instances there is good evidence of exchange of muscle potassium for sodium. Representative data from these experiments are included in table 1B for comparison. It is important to observe that in these cited experiments the chloride content of the muscles remained normal. In contrast, there is a considerable increase in chloride in these muscles in nephrosis. The values found on the average, at least, might result from addition of about 200 cc. of edema fluid to potassium-depleted muscles with the expected increase in intracellular sodium. Further studies, especially on biopsy samples, are needed to delineate the nature of the potassium depletion and the location of the excess sodium, chloride and water.

The simultaneous occurrence of an influx of water, sodium and chloride and loss of potassium from muscle has been described under very different circumstances, namely, after injury to muscle, e.g., after burns or trauma by tourniquetting[6, 16, 17] or extreme cold.[18] Comparative analyses of muscles injured by tourniquet trauma are given in table 1B. Of further interest is the fact that animals and patients[19] with such severe trauma are oliguric, excreting urine low in sodium and chloride and high in potassium.[17]

In this connection, Opie[20] has recently shown that liver and kidney are isotonic with 0.3 molar, not with 0.15 molar saline. After toxic injury to liver or kidney, however, these tissues become isotonic with solutions of lower molarity ranging down to 0.15 molar. Thus this tissue injury is associated with hypotonicity. The present investigators have made similar observations with muscle and found that after tourniquet injury, leg muscles as measured by Opie's technic appear hypotonic and reveal the analyses given in table 1B.

Since most of the body potassium is located in the skeletal muscles,[21] these data suggest that from one-fourth to two-thirds of total body potassium may have been dislodged and carried away, representing losses of from 1000 to 2400 mEq. potassium in an adult. These marked decreases in intracellular cation may be indicative of more important metabolic alterations involving intracellular anions, such as creatine-phosphate, adenosine triphosphate, desoxy- or ribose nucleic acids and other nucleates which occur within cells as potassium salts. Inasmuch as the K:P ratio in many of these substances is 2:1 or higher, less reduction in phosphate is understandable.

These data also permit speculations which throw light on the location of the edema. If the conventional calculations[4] to demarcate the intra- and extracellular phases are applied, the calculated values for intracellular water are so low in the face of the nitrogen and phosphorus values that one is inclined to suggest that in these tissues some of the extracellular ions sodium and chloride and some of the increased water may be intracellular. When the water content of muscle increases from the normal of 78% to 85%, 1.0 kg. of normal muscle becomes 1.47 kg. of edematous muscle. Inasmuch as one third of total body mass is muscle, when the body weight of the nephrotic child increases from 40 kg. to 60 kg. by edema formation, approximately one third of this increase may result from muscle hydration.

In previous studies,[1] balance data showed that in some patients with massive anasarca, a relative excess of chloride was jettisoned during diuresis which removed every vestige of edema. Because the muscle potassium is markedly subnormal when water, chloride and sodium are mobilized, some sodium presumably remains to restore the muscle cation

concentration. The Na:Cl ratio of the departing fluid would then be approximately 1.0 compared to 1.3 for interstitial fluid in these patients. If this occurred then the net loss of chloride during diuresis would exceed the amount calculated on the assumption that all edema is composed of interstitial fluid with the electrolyte pattern of ascitic fluid. Review of these tissues analyses may thus offer an explanation for the variability of the urine electrolytes excreted by different patients during diuresis.

Finally, it is worth noting that studies of plasma and urine electrolytes of patients with edema caused by chronic congestive heart failure[22] suggest that tissues analyses might reveal similar alterations.

Summary and Conclusions

Analyses of skeletal muscles, obtained at autopsy from six children with the nephrotic syndrome, reveal losses of from one fourth to two thirds of their potassium content per unit dry weight or cell solids. Their phosphorus content is only moderately reduced. These muscles have gained large amounts of water, sodium and chloride in ratios approximating extracellular fluid.

The muscle values are compared with other types of potassium loss from muscle, e.g., after experimental potassium deprivation, desoxycorticosterone therapy, alkalosis and muscle trauma.

Since potassium is the intracellular cation, its depletion may be associated with important effects on intracellular anions, enzymes or catalysts and, together with cellular hydration and hypotonicity, contribute to the physiologic alterations found in this syndrome.

Analyses of kidneys from these patients reveal somewhat similar changes; liver, in contrast, showed minimal alteration.

Acknowledgment

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SPANISH ABSTRACT

Cambios Tisulares en el Sindrome Nefrótico; Demostración de la Perdida de Potasio

Un estudio analitico de musculos voluntarios obtenidos en la autopsía de seís niños con sindrome nefrotico, reveló una perdida de potasio entre ¼-⅔ partes del contenido total de potasio por unidad de peso seco o solidos. El contenido de fosfóro estuvo moderadamente reducido. Los musculos ganaron grandes cantidades de agua, sodio, cloruro, en cocientes (ratios) aproximados a los del fluido extracelular.

Estos valores en pérdida de potasio muscular, fueron comparados con otras formas de depleción potasica; por ejemplo, deprivación experimental de potasio, tratamiento con desoxicorticosterone, alkalosis y trauma muscular.

Debido a que el potasio es un catión intracelular, su depleción puede asociarse con otros efectos importantes de los aniones intracelulares, enzimas o agentes cataliticos, que conjuntamente con la hipotonicidad é hidratación celular, contribuyen a la producción de las alteraciones fisiologicas encontradas en este sindrome.

El analisis de riñones en estos pacientes reveló alteraciones similares a las encontrada en los musculos, en contraste con el higado, que solamente demostró cambios minimos.

630 West 168th Street

USE OF AUREOMYCIN AND PENICILLIN IN THE TREATMENT OF RUBEOLA IN THE PRE-ERUPTIVE AND EARLY ERUPTIVE PHASE

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THERE is increasing evidence that true virus diseases, such as varicella,[1] epidemic parotitis[2] and poliomyelitis,[3] and influenza,[4,5] are not influenced by any known antibiotics. Aureomycin has, however, been shown to be effective in some virus-like diseases; psittacosis,[6,7] lymphogranuloma venereum,[8,9] and primary atypical pneumonia.[10-14] In addition, Dowling[15] and Drake[16] treated 9 and 12 cases of rubeola, respectively, and believed that the results were favorable. These encouraging experiences prompted the present investigators to study the effect of aureomycin in a larger series of cases of rubeola. This study was carried out between February 15 and May 15, 1950, when a considerable number of measles patients in the early phase of the disease were being admitted to the Willard Parker Hospital.

Past experience with penicillin in the treatment of rubeola indicated that the complications were reduced to a minimum, but that the rubeola was not altered otherwise. Since these observations had not been made in a carefully controlled series of cases, it was decided to give penicillin to some children beginning in the pre-eruptive phase or on the first day of rash. This penicillin-treated group served the dual role of evaluating the penicillin effect on early rubeola and also served as controls for those treated with aureomycin.* A third group of children with rubeola were left untreated and these acted as controls for both of the treated series. The data on many of the untreated and some of the penicillin-treated patients were obtained from their hospital records and were not observed by the authors during their illness.

TABLE 1

DISTRIBUTION OF CASES IN 3 GROUPS ACCORDING TO AGE

Group	Age (yr.)					Total
	0–1	1–2	2–3	3–5	5–9	
Aureomycin	7	10	9	14	5	45
Penicillin	2	11	10	10	11	44
Untreated	3	5	7	16	12	43

The first 15 cases of pre-eruptive rubeola were all treated with aureomycin; later alternate cases were treated with aureomycin or penicillin or remained untreated. A total

From the Willard Parker Hospital, New York City.
(Received for publication June 28, 1950.)

* Aureomycin was supplied through the courtesy of Lederle Laboratories.

of 45 patients received aureomycin, 44 penicillin and 43 no therapy (see table 1) other than for complications.

The antibiotics were given to the patients immediately on admission and for a period of four days according to the following schedule: 1. Aureomycin (oral) 60 mg./kg./day divided into 4 equal 6 hourly doses. 2. Procaine penicillin in oil, 300,000 units in one injection daily. Treatment was extended for complications.

Table 2 shows the relationship between onset of treatment with penicillin or aureomycin and the appearance of the rash. The two groups differ mainly in that three-fourths

TABLE 2

COMPARISON OF AUREOMYCIN- AND PENICILLIN-TREATED CASES WITH RESPECT TO TIME OF INITIATION OF TREATMENT AND BEGINNING OF RASH

	Before rash				Day of rash
	5 days	3 days	2 days	1 day	
Aureomycin	2	2	6	22	11
Penicillin	0	1	1	6	36

of the aureomycin-treated patients were started on therapy in the pre-eruptive period or at the beginning of the rash, whereas four-fifths of the penicillin-treated patients were given their first dose of penicillin at the time of the beginning of the rash.

Each patient was seen by one of the authors on or soon after admission and followed daily during the patient's hospital stay. Daily notations were made as to the degree and severity of the general condition, temperature, malaise, rhinorrhea, photophobia, cough, type of distribution and extent of rash and complications. A complete blood count, urine examination and roentgenogram of the chest were obtained in 35 cases when aureomycin or penicillin treatment was started and again after treatment was discontinued.

RESULTS

Evaluation of the effect of the antibiotics was made by comparing the duration and intensity of the rash, temperature, rhinorrhea, photophobia, cough and complications in each of the groups. The duration of the signs and symptoms were calculated from the day of onset of the rash. These data are recorded in table 3.

TABLE 3

AVERAGE DURATION IN DAYS OF SPECIFIC SIGNS AND SYMPTOMS OF RUBEOLA AFTER FIRST APPEARANCE OF RASH

Sign or Symptom	Aureomycin	Penicillin	Untreated
Rash	2.5	2.5	2.3
Fever over 37.6° C.	2.2	2.8	4.2
Photophobia	2.5	3.0	2.8
Rhinorrhea	3.6	3.4	2.7

Rash: The average period of rash noted indicates the time from its first appearance through to its completion and until it began to fade. This was 2.5 days in the aureomycin-treated cases, 2.5 days in the penicillin-treated group and 2.3 days in the untreated. The pattern of the rash and its intensity were not altered.

Temperature: The course of the temperature and the manner in which it was influenced by therapy are revealed in charts 1 and 2 and table 4. Charts 1 and 2 reveal a scattering of the elevations beyond the fifth day after onset of the rash in the untreated

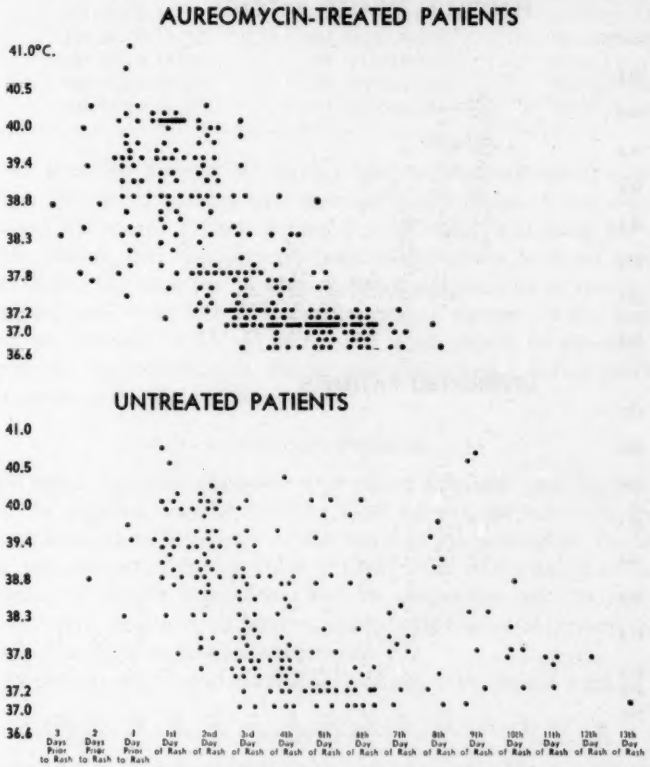

CHART 1. Temperatures of patients treated with aureomycin and of untreated control patients.

controls. These elevations were due to complications which occurred in 23%. There seems to be little or no significant difference in the group treated with aureomycin and that treated with penicillin. In both there was an earlier drop in temperature below 37.8° C. in many cases.

The average duration of fever (rectal temperature over 37.7° C.) after the appearance of the rash was 2.2 days in the aureomycin-treated patients, 2.8 days in the penicillin-treated group and 4.2 days in the control or untreated group. When subjected to statistical treatment using the highest single temperature recorded for each patient each

day, the mean temperature duration over 37.7° C. was found to be 3 days for the aureomycin group, 3 for the penicillin group and 6 days for the control group.

Photophobia: Photophobia lasted an average of 2.5 days in the aureomycin-treated group, 3.0 days with penicillin and approximately 2.8 days in the untreated series. Again the time was calculated from the first day of rash.

Rhinitis: The rhinitis lasted an average of 3.6 days after the onset of the rash in the aureomycin cases, 3.4 days with penicillin and 2.7 days in the untreated group. Of

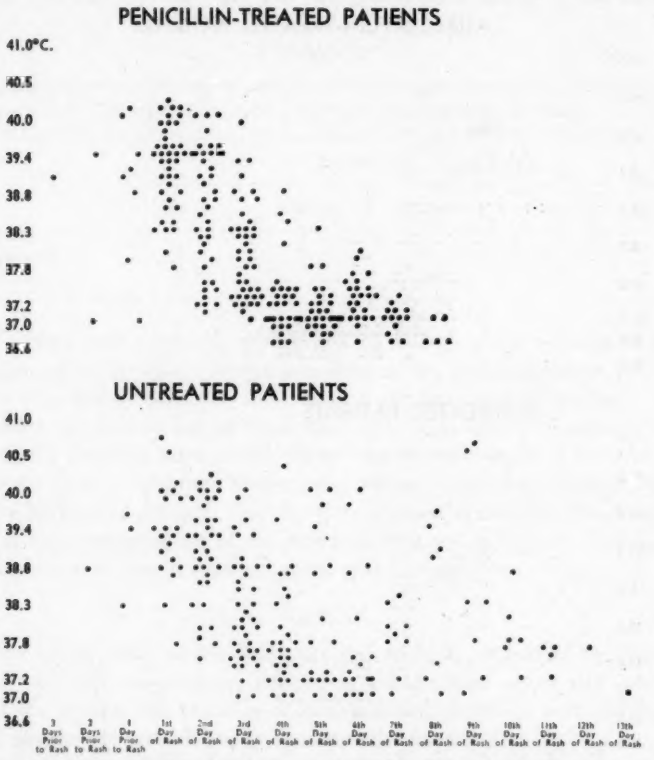

CHART 2. Temperatures of patients treated with penicillin and of untreated control patients.

the untreated group, only 8 patients were observed daily by the authors. The remainder of the controls were taken from the hospital records. Since records were incomplete, evaluation of the rhinitis and photophobia is not possible, but the impression gained was that they were not strikingly influenced by therapy.

Cough: Except for those untreated patients who developed pneumonia, the cough seemed to be of the same character and duration in all groups. Neither aureomycin nor penicillin reduced the cough appreciably.

Convalescence: The convalescence was usually uneventful in the patients treated with antibiotics. However, many complications prolonged convalescence in the untreated cases. In table 5 the complications are listed.

TABLE 4

VARIATION OF TEMPERATURE IN RELATION TO TREATMENT AND AGE OF RASH
Mean Temperatures Standard Deviation
(No. of cases)

Day of rash	Controls	Penicillin-treated	Aureomycin-treated
−1	only 3 cases	only 8 cases	102.61±0.15 (30)
1st	102.95±0.22 (20)	102.67±0.09 (41)	102.46±0.14 (40)
2nd	102.47±0.14 (36)	101.54±0.17 (41)	101.51±0.17 (40)
3rd	100.88±0.15 (37)	100.45±0.08 (40)	99.85±0.14 (38)
4th	100.29±0.14 (29)	99.12±0.09 (30)	99.21±0.1 (33)
5th	100.53±0.21 (18)	98.87±0.05 (27)	98.70±0.04 (31)
6th	100.01±0.18 (17)	99.14±0.05 (24)	98.49±0.00 (22)

Of the 43 untreated patients, 10 (23%) had complications which responded to chemotherapy. Of the 45 patients who were given aureomycin, 5 had complications when treatment was started (11%): 2 cases of otitis media, 2 of croup and 1 case of conjunctivitis. Shortly after therapy started, the complications, with the exception of croup, were cured. The latter two patients recovered after six days of aureomycin treatment. None developed complications during aureomycin therapy. Of the 44 penicillin-treated cases one patient (2.3%) had otitis media which cleared on penicillin. Another patient developed this complication during penicillin therapy and responded better when sulfonamides were added to the treatment.

LABORATORY FINDINGS

The blood counts taken on admission in 35 aureomycin- and penicillin-treated cases were within the expected range of 7,000 to 8,000 white blood cells with 45 to 75% polymorphonuclears, 25 to 53% lymphocytes, and 0 to 2% eosinophils. At the appearance of the rash the counts fell to 4,000 to 6,000 white cells with 10 to 20% polymorphonuclears, 70 to 80% lymphocytes and 4% eosinophils after the rash erupted. Urine findings were similar in all groups. Albuminuria was often present during the febrile periods. No case of nephritis was observed.

Of the 35 patients who had chest RGs on admission, 14 showed signs of hilar in-

TABLE 5

COMPLICATIONS OBSERVED BEFORE AND AFTER TREATMENT

Type	Aureomycin		Penicillin		Untreated
	Before	After	Before	After	
Otitis media	2	0	1	1	5
Pneumonia	0	0	0	0	3
Croup	2	0	0	0	1
Tonsilitis	0	0	1	0	1
Purulent conjunctivitis	1	0	0	0	0
	11%	0%	4.6%	2.3%	23.2%

filtration. Two days after aureomycin therapy was completed 5 patients showed no significant change, 3 demonstrated improvement, 2 were negative and 4 were not followed up. One patient with a negative RG on admission developed hilar infiltration during aureomycin therapy. Of 14 untreated patients, 6 had hilar infiltration at the time of admission, 3 of these became negative in 6 days and the others were unchanged at the time of discharge from the hospital.

Reaction to Aureomycin and Penicillin

In the series of 45 children who received aureomycin, 13 patients vomited their medication at least once on the second or third day of therapy. Although the same dosage was continued, the patients stopped vomiting. Diarrhea, which lasted a short time, occurred in three cases. Penicillin was generally well tolerated. Delayed penicillin reactions might have occurred after discharge.

Comment

Since only a few of the untreated control cases were observed by the authors, the information sought was obtained from the hospital records. While it was possible to obtain some reliable data, such as temperature, onset of rash, duration of rash, duration of illness and the complications, there were insufficient data on the degree and duration of photophobia, rhinorrhea and cough.

The data presented indicate that the main difference in the groups lies in the complications developed by the untreated control series and the resulting prolonged course in these cases. Aureomycin and penicillin tended to reduce temperature. When measured from the time of appearance of the rash it was 2.2, 2.8 and 4.4 days, respectively, in the aureomycin, penicillin and control group. The more rapid drop in temperature in the aureomycin-treated cases compared to the penicillin-treated group may possibly be explained by the earlier introduction of treatment in the aureomycin series.

The earlier drop in temperature in the treated cases seems to be significant when statistically evaluated. No direct evidence was obtained which would indicate an antibiotic effect on the signs and symptoms of rubeola, which could be associated with either the virus or the allergic phase of the disease. Therefore is it possible that aureomycin and penicillin actually interfered with secondary bacterial invaders which were present early in the rubeola and contributed to the temperature but did not create recognizable disease?

One of the authors (SK) had the opportunity to observe two children treated with aureomycin for five days prior to the appearance of the rash. The aureomycin seemed to have exerted no beneficial prophylactic effect. In both cases the rubeola followed the usual course. The same person has had similar experience with penicillin and sulfonamides given for respiratory infections prior to the development of rubeola. Again the rubeola seemed uninfluenced except that complications did not develop. Neither sulfadiazine nor penicillin were prophylactically effective against rubeola.

Conclusion

Neither aureomycin nor penicillin given to children with pre-eruptive rubeola or begun on the first day of rash seems to have any definite therapeutic effect on the course of the primary disease.

The temperature dropped earlier in the patients treated with aureomycin or penicillin than in the untreated control group.

Aureomycin and penicillin were effective against otitis media and pneumonia present on admission and on the complications which developed during the disease.

Aureomycin and penicillin are useful in the prevention and cure of secondary infection in rubeola.

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Spanish Abstract

Uso de la Aureomicina y Penicilina en el Tratamiento de la Fase Pre-eruptiva y Comienzo de la Fase Eruptiva del Sarampion (Rubeola)

La administración de aureomicina o de penicilina a ninos con sarampion (rubeola) en la fase pre-eruptiva o durante el primer dia de la erupción no tuvo efectos terapeuticos definidos sobre el curso de la enfermedad.

La temperatura cedió mas tempranamente en los pacientes tratados con aureomicina o penicilina que en el grupo de control.

Tanto la aureomicina como la penicilina fueron efectivas contra otitis media y pneumonias presentes en la admision del paciente al hospital, asi como en las complicaciones desarolladas durante el curso de la enfermedad.

Los autores señalan la utilidad de la aureomicina y penicilina en la prevención y tratamiento de las infecciones secundarias del sarampión.

888 Park Avenue

NEUROLOGIC COMPLICATIONS OF HERPES ZOSTER

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NEUROLOGIC complications of herpes zoster are rare in children.[1] Recently three such cases were observed, one of paresis of a leg and the other two of meningeal reaction. The first case contributes some evidence of the relation between varicella and herpes zoster.

Head and Campbell[2] reported 21 cases of herpes zoster in which autopsies were performed. The primary lesion in the nervous system was an acute round cell infiltration with areas of hemorrhage in the affected posterior root ganglions. There were changes in the posterior nerve roots and in the adjacent spinal cord but they considered these to be secondary degeneration. Wilson[3] stated that the pathologic changes were limited to the same regions but attributed the changes in the posterior root ganglions to a spread of the inflammation. He also described meningeal infiltrations, which explain the frequent occurrence of pleocytosis in the spinal fluid. Lhermitte and his collaborators[4] demonstrated more extensive pathologic changes. They found involvement of the spinal ganglions, posterior roots, peripheral nerves, posterior horns, gray matter of the anterior horns and the anterolateral columns. Lhermitte[5] described one case in which there were atrophic changes in the cells of the anterior horn with demyelinization of the nerve roots and some lymphocytic infiltration. In spite of this, there was no clinical paralysis.

Meningoencephalitis accompanying herpes zoster has been the subject of recent pathologic studies by Krumholz and Luhan[6] and by Hassin and Rabens.[7] They described the predominant changes as occurring in the pons and medulla, in combination with meningeal infiltration over the vertex and base of the brain including the basilar nerves.

Biggart and Fish[8] described perivascular lymphocytic infiltrations in the medulla, subcortical cerebellar nuclei, thalamus and hyperthalamus. They believe that initially there is involvement of the dorsal root ganglions. From there the inflammation spreads to the meninges of the spinal cord. The myelitic process may involve the anterior horn cells. The encephalitis, in their opinion, is merely the result of an upward extension of the virus along preformed pathways.

Krumholz[6] pointed out that the pathology of encephalitis following herpes zoster is different from that following varicella. In the latter, the perivascular infiltrations and degenerative changes are most marked in the cerebral and cerebellar white matter. In view of the possibility of herpes zoster and varicella being caused by the same virus, this is a most interesting observation.

Pathologic changes in the anterior horn cells that occur in herpes zoster explain the occurrence of motor complications. Taterka and O'Sullivan[9] recently reviewed the literature and reported 42 cases of paralyses accompanying herpes. They excluded facial palsies following otitic zoster and ocular palsies following ophthalmic zoster. They added two cases of their own and drew the following conclusions:

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1. Motor disturbances are rarely observed; middle aged and elderly people are most often affected; no cases in infants and children were recorded.

2. Of the 44 cases of paralysis, 20 involved the upper extremities, 18 the trunk muscles and 6 the lower extremities, including 2 cases of Carter and Dunlop[10] involving the quadriceps muscle.

3. The zoster eruption preceded the onset of paralysis in 75%, while it followed the paralysis in 25%. The interval between the eruption and the appearance of weakness varied from a few days to a few weeks.

4. In 100% the eruption and the paresis occurred on the same side. In 90% the segmental distribution coincided.

5. In 16% the patients recovered completely. In all others, there were varying degrees of residual weakness.

Encephalitis complicating herpes zoster is an unusual occurrence. Most reports have been of elderly adults, and the disease has had a uniformly fatal termination. Recently McCormick[11] recorded the case of a 4 year old child who recovered completely. The relationship of the appearance of the rash and the onset of meningo-encephalitis was variable. In most cases,[12] signs of involvement of the nervous system appeared after the onset of the eruption; following a case of herpes of the buttocks, symptoms appeared five weeks after the onset of the rash. Reports indicate, though not uniformly so, that the higher the neural segment involved, the sooner the appearance of symptoms. In most of the cases encephalitis complicated herpes which involved the cranial nerves, the cervical, or the upper thoracic segments of the cord. This coincides with the hypothesis of a direct upward extension of the pathologic process.

In an attempt to prove that zoster and the encephalitic process had a similar etiology, Schiff and Brain[13] obtained a positive complement fixation reaction between their patient's spinal fluid and the serums of the two zoster convalescents.

Report of Cases

Case 1. B.K., a 2 yr. old white female, was noted to be limping and favoring the left leg. She had no pain and apparently had not suffered any injury. The limp became more obvious during the next 4 days. On the 4th day, her mother noted an eruption over the left buttock, which she interpreted as a diaper irritation. From the time of onset until she was seen 5 days later, she had been afebrile and without symptoms except as previously noted. Past history was essentially negative.

Physical examination gave essentially negative results except for the neurologic findings in the left leg and the eruption on the left buttock. The extremities were of equal length, and there was no atrophy. There was weakness in extension at the left knee and hip. The left knee jerk was diminished, but the ankle jerk was normal. The left buttock was the seat of a vesicular eruption. Dr. S. C. Henn examined the patient and concurred in the diagnosis of herpes zoster, with paresis of the left leg.

During the next 2 wk. the limp gradually subsided, the left knee jerk returned to normal and the eruption faded. The child made a complete recovery.

Two weeks after the onset of herpes in this child varicella developed in her sister, D.K., aged 4 yr. Sixteen days later, or 1 mo. after the onset of herpes, B.K. also developed varicella.

Case 2. N.W., a 10 yr. old white male, complained of a frontal headache. He was drowsy and slept more than usual. He had a low grade fever up to 37.8°C. Three days later a rash, having "little blisters in it," appeared on the left chest and on the left shoulder posteriorly. Two days after the appearance of the rash, the temperature was 38.3°C. and rigidity of the neck and back was noted. The child was admitted to Sarah Morris Children's Hospital of Michael Reese Hospital on the service of Dr. Joseph K. Calvin.

Past history was essentially negative except for an attack of varicella 5 yr. previously.

Temperature was 37.8°C., pulse rate 92 and respiratory rate 20. In the distribution of the first and second thoracic nerves, left chest and shoulder posteriorly, there was an erythematous papular eruption with some vesiculation, a typical herpes zoster. The neck was moderately rigid, and Kernig and spine signs were positive. The spinal fluid was under a pressure of 240 mm.; opalescent fluid; Pandy 1+; cell count 597 with 100% lymphocytes; protein 62 mg.; chlorides 570 mg.; glucose 55 mg. A diagnosis of meningoencephalitis complicating herpes zoster was made.

Signs of meningeal irritation disappeared in 72 hr., as did the fever. The day after admission decreased superficial sensation was noticed in the area of the skin lesions. There was intense itching but no pain. The child was discharged on the 6th hospital day. Recovery has been complete with no sequelae.

Case 3. R.S., a 12 yr. old white male, complained of a sore throat. His temperature was 37.6°C. The next day the sore throat had disappeared, but the child complained of a moderately severe headache. The following day, a patch of small papules was noted on the left anterior abdominal wall in the region of T10. Additional crops appeared during the next 2 days in the same general area. There was no pain or itching. The fever remained low grade, headache persisted, and some nuchal rigidity was noted. Aureomycin was given at home with no apparent improvement. On the 7th day, the child was admitted to the Sarah Morris Children's Hospital of Michael Reese Hospital on the service of Dr. Joseph C. Greengard.

Past history was essentially negative except for an attack of varicella in 1943.

Temperature was 38.3°C. orally, pulse rate 88, and respiratory rate 20. In the distribution of T10 on the left side anteriorly there was an erythematous papular eruption with vesiculation, a typical herpes zoster. The neck was moderately rigid. The spinal fluid: Pandy 4+; sugar 29 mg.%; and 380 cells, 86% lymphocytes, and 14% polymorphonuclears. A diagnosis of meningoencephalitis complicating herpes zoster was made. The child was hospitalized for 3 days. During his hospital stay, a low grade fever persisted, but the nuchal rigidity and headache gradually disappeared. Recovery has been complete with no sequelae.

Relation Between Herpes Zoster and Varicella

Case 1 presents the problem of the interrelation of herpes zoster and varicella. Two questions arise: 1. Are the two diseases of different etiology, or are they caused by the same virus? 2. Are all forms of herpes zoster caused by the same virus, or is only one form caused by the virus of varicella? Most investigators agree that until the specific virus or viruses of the two diseases have been isolated and studied, no conclusions can be reached. However, clinical, serologic and cytologic investigations have shed some light on the subject. The results of these investigations are patent in the arguments put forward by the monists and the dualists in support of their respective views.

The dualists base their contention that herpes zoster and varicella are different disease entities on the following considerations:

1. Varicella produces immunity, so that a second infection or recurrence is rare.

2. Herpes zoster frequently develops in patients who have had varicella. Were herpes zoster and varicella caused by the same virus, this would be difficult to explain.

3. Herpes zoster protects against herpes zoster, but varicella may develop in patients who have had herpes zoster (Case 1).

4. The age susceptibilities of the two diseases differ appreciably. Varicella occurs most frequently in children, while herpes zoster is a disease of adults.

5. Herpes zoster, in contrast to varicella, is only slightly contagious.

6. Several epidemiologic observations seem to favor the view of the dualists. Cantor,[14] an English physician, reports that during 20 years' work on several small Pacific islands he saw many cases of herpes zoster but no cases of varicella. Stören,[15] a Norwegian

physician, worked five years in an isolated community and also noted many cases of herpes zoster but none of varicella.

The monists, headed by the French physician, Netter,[16] were aware of the apparent differences noted by the dualists but they attempted to explain these by postulating a mutation in the biologic characteristics of the virus; first in regard to its communicability (high in varicella, low in herpes zoster) and second in regard to tissue affinity (skin in varicella, nervous system in herpes zoster). The following evidence supports their view: 1. There have been so many cases of herpes zoster followed by varicella and varicella followed by herpes zoster that there can no longer be any doubt of the correctness of such observations. Although there are many reports showing a relation between the two diseases, the actual number of cross infections is relatively small. This is explained by assuming that herpes zoster may be caused by more than one virus and that varicella follows only those cases of herpes zoster caused by the virus of varicella. This theory would explain many of the discrepancies noted, but, as will be shown, it is probably not correct.

2. A cross complement fixation reaction resulting from the use of varicella antigen plus herpes zoster serum or herpes zoster antigen plus varicella serum has been demonstrated by Netter and Urbain.[17] This reaction takes place so frequently that Netter regards it as a constant phenomenon. The complement fixation reaction is not confined to ordinary herpes zoster alone but also in cases of symptomatic herpes zoster.

This indicates a common etiology for all cases of herpes zoster, the apparent primary agents acting as a stimulant to an otherwise latent herpes zoster virus. Netter concluded that herpes zoster is an infectious disease caused always by one definite, but still undetermined, virus. This virus is the same as that of varicella.

3. Experimental inoculations were attempted in 1922 by Kundratitz.[18] An unknown number of healthy children were inoculated with the fluid obtained from herpes zoster vesicles. In 20 a positive reaction, consisting of one or more varicella-like lesions with umbilication and surrounded by a red halo, developed at the site of inoculation in from 9 to 12 days. In five a generalized exanthem indistinguishable from varicella appeared 15 days after inoculation. On several occasions, varicella developed in previously healthy and unexposed children occupying the same rooms as those inoculated with zoster fluid. Among the children who had varicella and were inoculated with the fluid from herpes zoster vesicles, there were no positive reactions. Moreover, children who had a positive reaction did not develop varicella either when exposed to varicella or when inoculated with fluid from a varicella lesion. All children were under 6 years of age.

4. Brusgaard[19] studied the experimental lesions histologically and found them to be indistinguishable from those of herpes zoster and varicella. He concluded that while cytologic and serologic studies seemed to support a common etiology for the two diseases, proof would depend on the morphologic identification of the infective substances. To date these substances have not been cultured.

Discussion

Case 1 is the only case reported in the literature in which a motor complication following herpes zoster in children involved a segment of the body other than the face and eyes. The course of the disease in the first child was interesting from the following standpoints: 1. The paresis preceded the eruption by five days. This has occurred only in 25% of the reported cases. 2. The child recovered completely. This is an exception to the majority

of reports in the literature. 3. The absence of pain is unusual. None of the patients complained of pain at any time during the course of the disease.

Cases 2 and 3 are the second and third cases of meningeal reactions complicating herpes zoster in children in the literature. Here again, the signs of involvement of the nervous system antedated the cutaneous manifestations. The relatively mild course exhibited in both these cases and McCormick's case is in contradistinction to the uniformly severe course and often fatal outcome in adults.

The appearance of varicella four weeks after herpes zoster in the first case is interesting in light of the foregoing discussion. The patient's sister apparently contracted varicella following contact with her younger sibling; this is a frequently noted occurrence. If the two diseases have the same etiology, it is difficult to explain the complete lack of immunity to varicella that the patient showed such a short time after the development of herpes zoster. From a study of Case 1, there is no reason to modify Brusgaard's conclusion that proof as to the identity of the viruses of the two diseases depends on the identification of the infectious agents.

Summary

Three cases of neurologic complications of herpes zoster are reported. The relation of herpes zoster to varicella is discussed.

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SPANISH ABSTRACT

Complicaciones neurologicas del Herpes Zoster

Se reportan tres casos de herpes zoster que desarrollaron complicaciones neurologicas. Dos casos tuvieron reacciónes meningeas y un tercero desarrolló una paresia de la pierna izquierda. Esta última complicación motora, ocurrida en un niño, es el primer caso reportado en la literatura. Sé discute la relación entre el herpes zoster y la varicela. La prueba definitiva de la presencia de virus causantes de éstas enfermedades depende en la identificación de los agentes infecciosos.

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AUREOMYCIN IN THE TREATMENT OF MOLLUSCUM CONTAGIOSUM

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Iowa City, Iowa

AUREOMYCIN has been reported as effective in the treatment of molluscum contagiosum.[1] The purpose of this case report is to describe the response of a case of molluscum contagiosum to aureomycin in an infant.

CASE REPORT

A 20 mo. old white female infant was admitted to the hospital because of a skin rash which had appeared 2 wk. before and was becoming rapidly worse. Also there was a history of eczema appearing at the age of 2 mo. This had responded to treatment with a milk substitute and had not been present for the past few months.

On examination there was extensive involvement of the entire body, most marked on the extremities and genital areas, by waxy, whitish umbilicated papules from each of which a mucoid plug could be expressed. Some areas were excoriated from scratching. Physical examination was otherwise not significant. The blood count and urinalysis were normal.

Smears from 1 of the lesions stained with hematoxylin and eosin showed uniform homogeneous structures indicative of molluscum contagiosum.

Treatment was started with aureomycin 250 mg. every 6 hr., and moist boric acid protective dressings. One day after treatment was started the papules had begun to exfoliate and disappear. In 2 days the typical lesions had completely disappeared leaving a circular macular reddish base. On the fifth day the site of the papules had become pigmented and dry.

Some nausea was noted and aureomycin ointment substituted.

The infant was discharged on the seventh day with only small faint pigmented macules remaining.

COMMENT

The response of molluscum contagiosum to aureomycin in this case suggests that it is a simple and atraumatic method of treatment of this condition in infants and small children.

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SPANISH ABSTRACT

Aureomicina en el Tratamiento del Moluscuo Contagioso: Reporte de un caso

Una niña de veinte meses de edad fue admitida en el Hospital con una extensa erupción cutánea consistente en pápulas céreas, blanquecinas, umbilicadas.

Los frotis indicaron moluscuo contagioso.

Se prescribió aureomicina oral en dosis de 250 mgm. cada seis horas.

Al día siguiente las pápulas habían comenzado a desaparecer, y a los dos días las lesiones típicas habian desaparecido. Al quinto día la aureomicina oral fue sustituida por ungüento de aureomicina, debido a la aparicion de nausea. La niña fue dada de alta el séptimo día con solamente algunas máculas secas y ligeramente pigmentadas.

La aureomicina ofrece un tratamiento simple e inocuo del moluscuo contagioso.

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(Received for publication July 5, 1950.)

ELECTRIC BUNTING TO MAINTAIN BODY TEMPERATURE DURING EXCHANGE TRANSFUSION IN THE NEWBORN INFANT

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THE maintenance of proper body temperature has been a serious problem in the performance of exchange transfusions on newborn infants suffering from hemolytic disease. Many of these infants are in such poor condition that extreme care in their handling is required, including incubation, oxygen and tracheal aspiration. The many procedures necessary create the hazard of prolonged exposure to room temperature, and a number of deaths may have resulted directly or indirectly from hypothermia. In the Children's Hospital in Boston, the entire exchange transfusion is carried out with the infant lying in a Hess bed;[1] this is an ideal situation which undoubtedly is not readily available in most institutions where an exchange transfusion must be performed. The maintenance of body temperature with electric heating pads and/or hot water bottles has proved cumbersome and unsatisfactory, and has resulted in a number of burns, particularly about the buttocks.

A washable electric blanket bunting has been designed (see Figs. 1 and 2) to maintain the temperature of newborn infants throughout the procedure of an exchange transfusion, as well as for a period following the procedure, if a heated crib is not available. This bunting was constructed by the General Electric Company using water-proof washable material and employing the principles of the commercial electric blanket. The bunting can be regulated to any desired temperature although the maximum temperature obtainable is 42°C., which avoids the possibility of skin burns. The design of the bunting is simple: it is a bag with a zipper along one side to allow for easy insertion and removal of the baby, and a "U" shaped zippered flap which can be opened to provide a window at the approximate position of the umbilical cord. The top of the bunting is closed by a series of four ribbon ties. The electric circuit contains a step down AC transformer which produces a low voltage current. A small rheostat controls the current so that the temperature of the bunting may be regulated as desired. The zippered flap over the umbilical cord allows for the performance of the umbilical vein method of exchange transfusion with the maintenance of a controlled temperature within the bunting.

Parenteral fluids can be administered during any operative procedures by bringing the tubing through the top of the bunting or through the zippered side. After the operation, the flap is closed by the zipper and the child may be left within the bunting until it can adequately maintain its own body temperature. The bunting may also be used for the maintenance of proper body temperature of premature infants.

The authors have used the bunting during exchange transfusions in 50 infants without fatality. The use of the bunting during the performance of an exchange transfusion lessens the chance of hypothermic shock and makes the entire procedure safer, simpler and easier for the transfusionist. Because of the ease with which this bunting may be used, because

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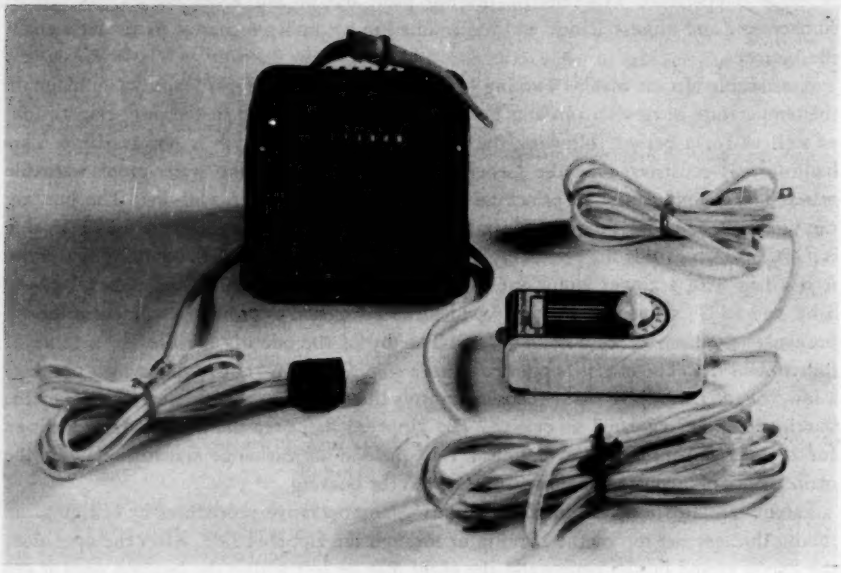

FIGS. 1 and 2. Infant's heated bag. Model No. P-314-5.

it is washable without the danger of a short circuit and because it is relatively inexpensive, it would seem to be useful for many circumstances where the body temperature must be maintained over indefinite periods.

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SPANISH ABSTRACT

Uso de la Manta Eléctrica para Mantener la Temperatura del Cuerpo Durante Transfusiones de Sustitución (Exchange Transfusion) en los Recién Nacidos

Se ha diseñado una manta eléctrica lavable para mantener la temperatura del cuerpo de recién nacidos durante una transfusión de sustitución asi como durante el período siguiente a la transfusión si no se dispone de una cuna calefaccionada. Esta envoltura eléctrica puede usarse independientemente del lugar del cuerpo deseado para la transfusión. La manta ha sido manufacturada por la General Electric Company con materiales lavables y trabaja como las mantas electricas comerciales (110 volts, 60 cycle AC). Puede regularse a la temperatura que se desee, con un máximo de 42 grados Centígrado para evitar la occurrencia de quemaduras.

51 East 90th Street

BRAIN DAMAGE IN A JUVENILE DIABETIC PATIENT ASSOCIATED WITH INSULIN HYPOGLYCEMIA

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ONE complication of the treatment of diabetes mellitus in infants and young children is the relative ease with which some of these patients develop hypoglycemia. Juvenile diabetic patients may develop temporary or permanent cerebral damage from hypoglycemia produced by doses of insulin well within the therapeutic range.[1-7] The case presentation which follows has been unusually well documented from the psychometric point of view and provides quantitative data on the mental deterioration of such a patient.

CASE REPORT

The patient was an 8 yr. old white boy, R. B. (M.G.H. 387877), who had been known to have diabetes mellitus since the age of 22 mo. Birth history and early development were uneventful. The infant was weaned from the breast at 12 mo. and at age 22 mo. there was an episode of vomiting. At this time glycosuria was discovered and the diagnosis of diabetes mellitus was made. Inappropriate treatment with 16 units of protamine zinc insulin/day and a diet of 150 gm. carbohydrate, 70 gm. protein and 75 gm. fat/day was instituted by a physician in the clinic which the patient was then attending.

Shortly after insulin treatment with the excessive amount of protamine zinc insulin was begun, the infant had 2 severe hypoglycemic reactions at home, accompanied by generalized twitching. For the next 2 yr. he had hypoglycemic reactions approximately twice monthly with drowsiness and often with vomiting. These episodes could always be controlled before loss of consciousness by the oral administration of sweetened fluids. At age 3 10/12 yr. an attack of otitis media precipitated diabetic coma. He was admitted to another hospital where the blood sugar was 640 mg./100 cc. and the serum carbon dioxide content was 3 mEq./l. on arrival. A total of 210 u. of insulin was required in the treatment of the diabetic coma. The child was discharged on 160 gm. carbohydrate, 70 gm. protein, 80 gm. fat and the rather large dose of 12 u. regular insulin and 30 u. protamine zinc insulin/day. By age 5 yr. the child appeared to be well controlled on 8 u. regular insulin and 12 u./day protamine zinc insulin.

The child began school at age 5½ yr. and failed the first year twice because he "played all day and refused to learn to read and write." He was brought to the Massachusetts General Hospital for the first time at age 7 yr. for investigation of his inability to get along at school. The insulin dosage of 12 u. of crystalline and 16 u. of protamine zinc insulin which he had been receiving was found to produce hypoglycemia in the late mornings. Psychometric examination at this time revealed a Stanford-Binet mental age of 7 to 10 yr. with an I.Q. of 111 (an I.Q. of 108 was obtained by another examiner). The child had a 6 yr. record for putting pieces in place with 2 hands. On a performance test he had a mental age of 7 and 8 yr., with ranges up to a 10½ yr. score in some portions of the test. Tests showed almost normal spatial perception, but he could not read and had rather poor motor control. The child was lively, active, talkative and cooperative and showed good planning ability. An electroencephalogram showed bilaterally diffusely scattered 4, 5 and 6/sec. waves which were judged to be abnormal for his age (Fig. 1A). A psychiatric consultant commented that the picture "presents a combination of a conduct disturbance and a defect in certain cognative functions, such as reading and the recognition of numbers and pictures."

The child was discharged to an institution in his home state for care of his behavior problem.

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At this time his I.Q. was found to be 105. The reduced dosage of insulin on which he was discharged still proved excessive, as soon after reaching this institution he had a grand mal type of convulsion, apparently associated with hypoglycemia and followed by drowsiness and nausea. Two months later, at the age of 7 10/12 yr., a similar episode occurred. There was an insulin reaction in the early morning, followed by a generalized convulsion at 1 p.m. in which the child's eyes and face were drawn to the right, and the pupils were dilated and there was twitching of all extremities.

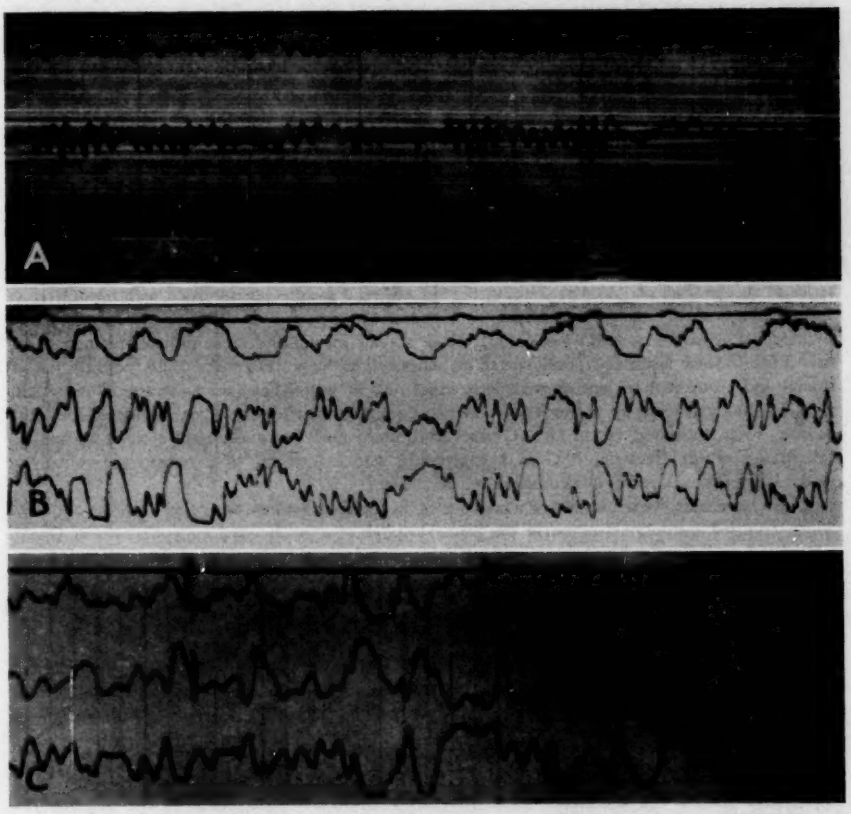

FIG. 1. Occipital recordings from EEGs done at ages 7 yr. (1A), 7 10/12 yr. (1B) and 9 yr. (1C). First tracing (1A) was considered abnormal because of amount of random waves at 4 to 6/sec. Progressive deterioration can be seen in remaining tracings. Technical data: Each division of horizontal line at bottom of Fig. 1A = 1 sec. Scale is same for other 2 tracings. Such division placed vertically on 1A and 1B = 250 microvolts.

He responded promptly to the intravenous injection of 50% dextrose in water. Unfortunately, but little change was made in insulin dosage and a third such episode occurred 2 wk. later, after which the child spoke only a few words and seemed unable to carry out directions involving motor coordination. Sodium dilantin, barbiturates and amphetamine did not help. He was then admitted to the Massachusetts General Hospital for re-evaluation.

Although only 10 mo. had passed since his first psychometric evaluation, there was obvious evidence of gross brain damage. Psychometric testing by the same examiner revealed marked deterioration. The child responded only with "yes" or "no" to questions. When shown what was desired by gestures he was very cooperative. Language comprehension was at the 2½ yr. developmental

level. Motor speed was 5 to 6 yr. and spatial perception 3½ yr. Performance was so poor that no attempt was made to calculate an I.Q.

An EEG done at this time was interpreted as strikingly worse than the preceding tracings, showing progressive pathologic changes probably involving the electric activity of the whole left cortex (Fig. 1B).

Outstanding features of this deterioration were increase in diffuse slow activity with slowing and reduction in amount of regular activity ("alpha activity") posteriorly. There was also a progressive contrast between the 2 sides of the head, with reduction of voltages and reduction in well-defined wave forms on the left side of the head. These latter effects were apparent in the occiput at the onset and became progressively more extensive until they were finally noted in the left postfrontal region. Air encephalogram showed definite enlargement of the lateral ventricles and the third ventricle. A photograph of one of these roentgenographic films has been recorded elsewhere.[8]

Regulation of the child's diabetes mellitus was difficult in that falls in blood sugar that ordinarily would have produced no symptoms were associated with seizures. There were 6 instances of convulsive seizures during this stay, in only one of which the blood sugar concentration dropped as low as 45 mg./100 cc. (ferricyanide method of Folin).

One year later, at age 9 yr. a psychometric test by the same examiner revealed a nearly mute boy who cooperated with pleasure on simple performance tests. He performed the Merrill-Palmer series at an age level of 3 to 4 yr. During the test he had 4 seizures unassociated with hypoglycemia, each lasting about 5 min. His medication consisted of 195 mg. sodium dilantin, 195 mg. N-methyl-5-ethyl-5-phenylbarbituric acid (mebaral®), 16 u. regular insulin and 20 u. protamine zinc insulin/day. EEG showed continued development of abnormalities (Fig. 1C). The right but not the left frontal and postfrontal regions showed paroxysmal runs of well-defined waves to around 2/sec. and probably 200 microvolts or more. These alternated roughly with lower voltage 24/sec. spikes. This activity is not illustrated, but in Fig. 1C traces of it can be made out in the right occiput. For graphic comparison of the abnormal EEG in hypoglycemia with the tracing of a normal individual, the reader is referred to a recent clinicopathologic conference.[9]

During the next 2 yr. in spite of avoidance of hypoglycemia there was progressive deterioration which required institutionalization in the State Hospital as a deteriorated epileptic patient. One to nine grand mal and 30 to 40 petit mal attacks occurred monthly in spite of large doses of anticonvulsants. He died at 12 yr. of age following a convulsion and subsequent coma.

Discussion

Several clinical reports have described the association of insulin hypoglycemia in juvenile diabetes with psychiatric disturbances or brain damage.[1–7] Animal experimentation has shown that an excess of insulin produces organic cerebral lesions[10,11] and depletion of brain glycogen.[12] It is of clinical interest that experimental hypoglycemia in animals appears to affect first the higher centers of the cortex, next the upper part of the brain stem, and finally the medulla.[13] The march of signs and symptoms in the patient just described, as well as in other cases in the literature, compares favorably with these experimental observations. The patient reported here showed first a conduct disturbance at age 5½ years with an average I.Q. at that time. Anderson's "Case II" was a juvenile diabetic patient who had many hypoglycemic attacks and developed tantrums and destructive tendencies at age 7 years. His I.Q. was found to be 62.[4] The later development of recurrent convulsive seizures and gross mental deterioration in the present authors' patient is reminiscent of Anderson's "Case I," a 13 year old diabetic patient who developed "gross dementia" and an I.Q. of 43,[4] and Layne's and Baker's 8 year old diabetic patient who became an "idiot" after a prolonged episode of hypoglycemia.[3] The aphasia associated with a seizure in the present authors' patient is similar to that of the 6 year old diabetic child reported by Allan and Crommelin who developed aphasia, hemiplegia and convulsive episodes for over a year after an insulin reaction.[5] The error of mistaking

insulin shock for diabetic acidosis has apparently caused the death in hypoglycemic convulsions of at least two juvenile diabetic patients.[1,7]

The foregoing clinical data serve to emphasize the potential hazards of insulin hypoglycemia in the treatment of juvenile diabetes mellitus. The physician who cares for infants and children with diabetes mellitus should exercise caution that the insulin therapy while controlling the hyperglycemia does not result in periods of harmful hypoglycemia. Young children and infants on a moderately liberal carbohydrate diet seem to be better on insulin therapy providing a higher ratio of crystalline to protamine zinc insulin than is commonly used for adults. The use of protamine zinc insulin alone or too high a ratio of protamine to crystalline insulin is a not uncommon cause of severe hypoglycemic reactions in children. If both insulins are being given before breakfast, the addition of crystalline insulin before supper appears preferable to dependence upon large doses of protamine zinc insulin to control evening hyperglycemia.[14]

Summary

Clinical data are presented on a child with diabetes mellitus who developed, in association with repeated episodes of insulin hypoglycemia, progressive mental deterioration and organic brain damage which ultimately led to epileptiform seizures unassociated with hypoglycemia.

The implications of these findings are discussed and similar cases in the literature are reviewed.

Acknowledgment

Acknowledgment is made to Dr. John A. Abbott of the Massachusetts General Hospital Brain Wave Laboratory who reviewed and interpreted the encephalographic findings and organized the data in figure 1 and to Dr. Elizabeth Hincks who performed all the psychometric tests reported on this patient.

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SPANISH ABSTRACT

Lesión Cerebral en un Diabético, Producida por Hipoglicemia Insulínica

Se describe un caso que demuestra la facilidad relativa con que diabéticos jóvenes pueden desarrollar lesiones cerebrales debidas a reacciones hipoglicémicas secundarias al uso de insulina. En este caso, la diabetes comenzó a la edad de 22 meses, presentándose distintos ataques de hipoglicemia debidos al uso exclusivo de la insulina protamínica. A los siete años de edad, la edad mental del paciente era de siete a diez años, pero este ya presentaba un electroencefalograma anormal y su conducta ya resultaba un problema. Estas reacciones hipoglicémicas continuaron ocurriendo y diez meses después, el paciente presentó trastornos mentales importantes con deterioro de la comprensión del lenguaje, que retrocedió al nivel de los dos años y medio. Desde ese momento, el paciente comenzó a tener ataques convulsivos sin relación alguna con la hipoglicemia y falleció a los doce años de edad, después de una convulsión.

Se señala que los diabéticos jóvenes responden mejor a un tratamiento de insulina que contenga una proporción mas alta de insulina cristalina en relación con la insulina-zinc-protamina, que la proporción que se usa corrientemente en el tratamiento de los diabéticos adultos.

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THERAPY OF TUBERCULOSIS IN INFANTS AND CHILDREN

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ALTHOUGH mortality rates from tuberculosis have shown a persistent decline over the past 50 years,[1] this disease still remains a significant cause of death in all age groups of infancy and childhood beyond the neonatal period. The declining mortality from tuberculosis began long before any effective antibacterial agents were available against the tubercle bacillus. The introduction of various therapeutic agents during the past 10 years apparently has not significantly altered these declining mortality rates.

Certain sulfones such as promin®, diasone®, promizole® and sulphetrone® have been shown to have considerable tuberculostatic effect by *in vitro* and *in vivo* experiments.[2–5] Improvement, but usually not complete cures, have followed the use of these agents in clinical trials.[6] Other organic chemicals, such as para-amino-salicylic acid (PAS)[7] and the various thiosemicarbazones,[8] have likewise given promise of being useful tuberculostatic agents. Sufficient clinical studies have not yet been completed to accurately evaluate their place in the therapy of tuberculosis. The use of the preceding agents is limited by their relatively low therapeutic effectiveness and by various toxic side actions. None, moreover, can be considered curative when used alone.

There is no doubt that the most effective agent against M. tuberculosis is streptomycin or its derivative, dihydrostreptomycin.[9–11] That each of these drugs has a significant tuberculostatic effect cannot be doubted. The use of either drug is limited, however, by the various toxic manifestations, the most serious being temporary or permanent damage to either the vestibular or cochlear portions of the eighth cranial nerve and, more important, by the emergence of resistant tubercle bacilli.

Neomycin, an antibiotic recently reported by Waksman,[12] is currently under clinical trial. At present, its value is unestablished. Moderate toxicity is anticipated from this agent.

It seems well established at present that the effectiveness of streptomycin is enhanced by the concurrent administration of some other agent.[13] Promizole® and PAS have been most widely used to increase the tuberculostatic effect of streptomycin. Moreover, the concurrent administration of either of these agents reduces the frequency with which streptomycin-resistant tubercle bacilli develop during therapy.[11]

A combined effort by individual groups as well as by cooperating investigators has been put forth during the past few years in an effort to define the exact usefulness of the preceding agents in the treatment of tuberculosis. Most of the studies[9–11] have been undertaken with adults. Scattered reports of the treatment of tuberculosis in infants and children have appeared. Most of the latter reports deal with the effectiveness of streptomycin or dihydrostreptomycin in the treatment of miliary and meningeal tuberculosis.[14–22]

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TABLE 1

TUBERCULOUS MENINGITIS

Case	Other T.B.		Treatment								Cond. at start of Rx.	Diagnosis		Remarks
			Elsewhere				Coop. Clinics							
	Miliary	Other	Days[1]	S'M.[2] gm.	I.T.[3]	Other[4]	Days[1]	S'M.[2] gm.	I.T.[3]	Other[4]		CSF Cult.	Autopsy	
1. WM 12/12	0	+	0	0	0	0	47	94	46	0	Moribund	0	Died None	Progressive deterioration. Hydrocephalus.
2. WM 4- 0/12	+	+	0	0	0	0	214	214	62	Dias.	Fair	+	+	Relapse 47 days after 183 days Rx. Died 43 days later. Hydrocephalus.
3. WF 1-11/12	0	+	0	0	0	0	8	8	8	0	Poor	+	Died None	Progressive deterioration.
4. NM 8-10/12	0	+	0	0	0	0	316	583.8	157	Dias. PAS Prom.	Poor	+		Relapse 62 days after 143 days of Rx. Seems good 256 days after 168 days of re-treatment. Occasional convulsions since Rx. discontinued.
5. NM 9- 3/12	0	+	0	0	0	0	38	25.1	21	PAS	Poor	+	+	Progressive deterioration. Hydrocephalus.
6. WM 1- 2/12	0	+	0	0	0	0	7	2.5	5	PAS Prom.	Poor	+	+	Progressive deterioration.
7. WF 1- 2/12	0	0	0	0	0	0	8	2.7	6	PAS	Moribund	+	Died None	Progressive deterioration.
8. WF 1- 3/12	0	+	0	0	0	0	3	0.85	3	PAS Prom.	Moribund	+	+	Progressive deterioration.
9. WF 4- 9/12	+	+	0	0	0	0	112	132.2	50	PAS	Fair	+	+	Temporary improvement. Miliary lesions cleared. Hydrocephalus.
10. WM 12/12	+	+	12	7.2	0	0	221	221.9	122	PAS PROM.	Poor	+		Miliary cleared. Relapsed 247 days after 84 days Rx. Seems good on 137th day of Rx. for relapse.
11. NF 1- 1/12	+	+	3	1.25	3	0	115	59.5	63	PAS	Moribund	+	+	Decerebrate for 135 days. Hydrocephalus. Miliary cleared.
12. NF 2- 6/12	+	0	55	At least 20	0	Prom.	84	72.1	46	PAS. Prom.	Fair	+	+	Progressive deterioration. Hydrocephalus. Miliary cleared.
13. WM 2- 3/12	0	+	0	0	0	0	109	43.6	54	Prom.	Fair	+	Died None	Progressive deterioration. Hydrocephalus.
14. WM 6/12	+	+	0	0	0	0	126	87.4	69	PAS.	Poor	0		Seems good 309 days after 126 days of Rx. Miliary cleared.
15. WF 2- 3/12	0	+	0	0	0	0	9	16.5	7	PAS.	Moribund	+	+	Death from massive hemorrhage from duodenal ulcer.
16. WM 1- 3/12	0	+	0	0	0	0	38	32.7	21	PAS.	Moribund	+	+	Progressive deterioration.
17. WF 12- 6/12	+	0	134	134	8	0	4	15.2	6	PAS. Prom.	Moribund	+	+	Progressive deterioration. Meningitis developed while under Rx. elsewhere for miliary. Miliary cleared.
18. WM 9- 8/12	0	+	0	0	0	0	126	323.1	69	PAS. Prom.	Fair	+		Left hemiplegia, improving, 85 days after 126 days of Rx.
19. WM 11/12	+	+	0	0	0	0	126	96.6	88	PAS.	Fair	+		Deteriorating. Hydrocephalus. Miliary clearing.
20. WM 1- 2/12	0	+	0	0	0	0	89	89	47	PAS. Prom.	Moribund	+	Died None	Progressive deterioration. Decerebrate for 109 days. Hydrocephalus.
21. WF 1- 1/12	0	+	15	15	0	0	5	4	4	PAS.	Moribund	+	+	Progressive deterioration.
22. WM 10/12	+	+	0	0	0	0	12	12.8	8	PAS.	Fair	0		Rx. started 12 days ago.

[1] No. of days of streptomycin therapy.

[2] Total grams of streptomycin intramuscularly.

[3] No. of intrathecal injections of streptomycin.

[4] Dias.—diasone.

PAS—para-amino-salicylic acid.

Prom.—promizole.

Few reports concerning the effectiveness of the various antibacterial agents in the treatment of other types of tuberculosis in infants and children have been presented.[23, 24]

The difficulty in establishing the exact usefulness of these agents in adults with tuberculosis[9-11] indicates clearly that none of the present agents is sufficiently effective. It is not surprising that the indications for the treatment of tuberculosis in infants and children are not clearly defined since such problems in the therapy of tuberculosis in adults remain unsolved after the careful study of thousands of patients. Few results of the antibacterial treatment of infants and children with tuberculosis are reported. The decreasing frequency of tuberculosis in the younger age groups makes it difficult for varied and extensive experience to be gained by individual studies. In infants and children the extreme variability in the natural course of most types of tuberculosis, other than miliary and meningeal, is well recognized. The greater tendency towards the slow, but spontaneous healing of tuberculosis in infants and children makes evaluation of therapeutic agents extremely difficult.

The present report is made in the hope that it will help in evaluating the usefulness of the present antibacterial agents used in the therapy of various types of tuberculosis in infants and children.

Tuberculous Meningitis

The most severe form of tuberculosis, tuberculous meningitis, has received the greatest amount of attention. Since the first case in the present group was treated in the fall of 1946, 21 additional patients have been studied (table 1). With the exception of Cases 18 and 21, all cases have been treated in one of three Philadelphia hospitals (Temple University Hospital, St. Christopher's Hospital for Children, or Philadelphia Hospital for Contagious Diseases*). The patients described in the table represent all admissions to the pediatric service in these hospitals in whom the tentative diagnosis of tuberculous meningitis was made before death. Treatment was undertaken in all patients regardless of previous therapy and regardless of the condition of the patient at the time therapy was instituted. In brief, then, no patient in whom the diagnosis of tuberculous meningitis was made was excluded from streptomycin therapy for any reason. It is felt that this policy has put tuberculostatic agents to a severe test.

Of the 20 patients treated in these hospitals, five are still alive although streptomycin therapy has been discontinued in only two. One of two patients treated in other hospitals is alive after streptomycin therapy has been discontinued. Thus, 6 (27.3%) of the patients are alive, although only 3 (13.7%) have had therapy discontinued. On March 15, 1950, the latter three patients were alive 85, 256 and 309 days, respectively, after streptomycin therapy was completed. The total period of treatment for these patients, respectively, was 126, 311 and 126 days. Of the three patients under treatment on March 15, 1950, one seems to be in good condition after 221 days of treatment, one patient is deteriorating and has an extremely poor prognosis on the 126th day of treatment whereas treatment in the remaining patient is in the twelfth day at the time of writing. The outlook for this last patient is, of course, unpredictable at the present time.

The patients who no longer receive streptomycin are in relatively good condition. Case 14 is apparently normal without residua. Case 4 is in apparently good health, although

* All patients treated at the Philadelphia Hospital for Contagious Disease were on the service of Louis Cohen, M.D.

From.—promizole.

he has had occasional convulsive episodes following the cessation of therapy. In the interims between convulsions, no significant neurologic abnormalities have been noted. The remaining patient, Case 18, had severe left-sided hemiplegia at the time treatment was started. The hemiplegia is still present but has shown significant and progressive improvement.

Of the patients who died, nine were deeply comatose and in decerebrate rigidity at the time treatment was begun and were regarded as being moribund at this time. The condition of three patients prior to the start of therapy was regarded as poor, i.e., they were comatose, but not decerebrate and had marked signs of meningeal irritation, including various palsies; they also had marked systemic manifestations of infection. Four patients were apparently in fair condition prior to the start of treatment. They were responsive to external stimuli but showed some clouding of the sensorium along with mild to moderate signs of meningeal irritation and mild to moderate systemic reactions.

Five of the 16 fatal cases had associated miliary tuberculosis and three of these had other demonstrable tuberculous foci. In 10 patients, no miliary tuberculosis was noted, although other tuberculous foci were present. The remaining patient showed no demonstrable tuberculosis other than meningitis. It seems reasonable to state, therefore, that all but one of these patients had extensive tuberculous infections other than meningitis.

At the start of therapy the condition of the surviving patients was regarded as being poor in three instances and fair in the remaining three instances. None was regarded as being moribund at this time. All had demonstrable tuberculosis other than meningitis; four showed miliary tuberculosis. Thus, these patients likewise showed extensive tuberculosis other than meningeal infection.

The diagnosis of tuberculous meningitis seemed certain from clinical observations in all patients and was confirmed by the isolation of M. tuberculosis by culture from the spinal fluid one or more times in 19 of the 22 patients. In only one of the fatal cases, Case 1, were no positive spinal fluid cultures obtained. This patient showed a concentration of sodium chloride as low as 628 mg./100 cc. in the spinal fluid, positive culture from the gastric contents and extensive pulmonary lesions. No positive spinal fluid cultures have been obtained from two patients who are alive at present. Case 22 has only recently been studied and sufficient time for the growth of M. tuberculosis has not elapsed. The other patient who remains alive, Case 14, from whose spinal fluid no tubercle bacilli have been isolated, had typical clinical findings of meningitis, extensive lobar tuberculous pneumonia associated with miliary lesions, close contact with an infected adult in the household, and a concentration of sodium chloride as low as 520 mg./100 cc. in the spinal fluid. Therapy consisted only of streptomycin and para-amino-salicylic acid. Although a positive diagnosis of tuberculous meningitis cannot be made absolutely, it seems unlikely that the meningeal infection was caused by any agent other than M. tuberculosis.

Autopsy examination of 11 of the 16 fatal cases showed significant hydrocephalus in all instances. The obstruction to the flow of cerebrospinal fluid was produced by extensive collections of exudate at the base of the brain and in some instances also by tuberculomata which occluded the third or fourth ventricle. Several of the patients showed extensive tuberculous arteritis with large areas of encephalomalacia. In all instances tuberculous foci were demonstrated in the lungs.

Therapy

The therapeutic programs have varied somewhat in this group of patients. All patients other than Cases 1, 2, 3 and 13 have been treated according to a plan of therapy developed by a group of investigators representing several cooperating clinics and the Therapeutic Evaluation Section of the Tuberculosis Control Division of the U. S. Public Health Service. The details of this program will be reported by the cooperating group of investigators. The intramuscular doses of streptomycin employed under this program were 20 mg./kg. every 12 hours or 50 mg./kg. every 12 hours. Intrathecal administration of streptomycin was 2 mg./kg. in those patients receiving the former intramuscular dose of streptomycin and 50 mg., regardless of weight, in those receiving the larger dose. Under either plan, treatment was undertaken for courses of 42 days separated by rest periods of 10 days. Eighty-four intramuscular and 23 intrathecal injections of streptomycin constituted a course of therapy. Para-amino-salicylic acid was administered orally in daily doses of 0.2 gm./kg. When promizole® was used it was given in doses up to 2 gm./day or in doses sufficiently large to yield a concentration of promizole® in the blood of 1 to 3 mg./100 cc. The four patients who were not part of the cooperative study, Cases 1, 2, 3 and 13, received intramuscular streptomycin in daily doses of approximately 200 mg./kg., 70 mg./kg., 90 mg./kg. and 40 mg./kg., respectively. Thus, all but Patient 1 received doses in the range of that administered to patients in the cooperative study. All patients except Cases 1 and 3 received some other tuberculostatic agent in addition to streptomycin.

Only those patients who received relatively large doses of streptomycin are alive at the present time. Moreover, among the fatal cases, the duration of life was greater among those patients who received the larger doses of streptomycin.

Attention is directed to table 1 in which the number of days of treatment and the amounts of streptomycin administered intramuscularly as well as the number of intrathecal injections are noted.

The usual toxic reactions to streptomycin were noted in these patients. Vertigo, skin eruptions, eosinophilia, cylinduria and local reactions at the sites of injection were observed. One patient, Case 14, had a severe reaction to the intrathecal administration of 50 mg. of streptomycin. No serious reactions to para-amino-salicylic acid or promizole® have been observed. No patient who received promizole® has shown acceleration in the development of secondary sex characteristics. In addition, enlargement of the thyroid gland has not been noted in any of the patients treated with promizole®. The two patients who received diasone® showed anemia and occasionally cyanosis.

Bacterial Resistance to Streptomycin

Extensive studies of bacterial resistance to streptomycin have not been possible. In 10 of the 16 fatal cases such tests were made.* Of these patients, eight had studies of bacterial resistance made on specimens isolated from the cerebrospinal fluid before or close to the time treatment was begun. In the case of seven patients the tubercle bacilli were fully sensitive to streptomycin, but the organisms from one patient, Case 7, were markedly resistant although she had not received streptomycin previously. A full report of this patient will be made elsewhere.

* Most studies were made by Mr. William Steenken of the Trudeau Laboratory, Saranac, N.Y.

In 7 of the 10 patients, specimens obtained close to the time of death or at autopsy were studied. The organisms isolated late in the course of disease were fully sensitive to streptomycin in only three instances. In the other four instances luxuriant bacterial growth was noted in media containing at least 100 μg. of streptomycin/cc. These organisms are regarded as resistant. In five patients satisfactory serial resistance studies were possible. Three of the five patients showed that tubercle bacilli originally sensitive to streptomycin, ultimately became resistant to streptomycin in concentrations of at least 100 μg./cc. The observations that streptomycin-resistant tubercle bacilli were isolated from four patients during the terminal stages of meningitis or at autopsy and that streptomycin-resistant tubercle bacilli were found once in the specimen obtained prior to therapy would seem to be of considerable moment. Thus, in the small group studied, streptomycin-resistant tubercle bacilli were discovered in 5 of the 10 patients so examined. It should be noted, moreover, that all the patients who developed streptomycin-resistant tubercle bacilli received some tuberculostatic agent in addition to streptomycin.

Streptococcal Enzymes Intrathecally

Solutions of the enzymes, streptokinase and streptodornase,* were administered intrathecally on three occasions to each of two patients with severe chronic tuberculous meningitis. Administration of the enzyme solution was followed by immediate increase in irritability on each occasion, fever on four of six occasions, and convulsions once. Increased numbers of WBC and especially RBC were noted in the cerebrospinal fluid for 48 to 72 hours following administration of the enzymes. There is limited evidence that the level of streptomycin in the cerebrospinal fluid was increased for 24 to 72 hours after these enzymes were used. Neither patient showed any favorable response to these substances, but it must be clearly stated that both patients had been comatose and decerebrate for over a month before the preparations were used. There was, however, a suggestion that the cerebrospinal fluid flowed more freely following the use of these substances.

Miliary Tuberculosis

Treatment of miliary tuberculosis has been encouraging (table 2). Of 7 patients treated with streptomycin, 5 are living from 3 to 25 months from the start of treatment. All but two patients, Cases 6 and 7, had a known contact with a tuberculous adult in the home. The home contacts of the former patient could not be traced. The latter patient was born and lived in a Displaced Persons Camp until two months before symptoms were noted. Contacts presumably occurred there. All patients had positive tuberculin reactions and five had positive gastric or bronchial cultures. In only one patient, Case 1, was it impossible to demonstrate roentgenographic evidence of tuberculous lesions other than miliary in the chest.

The two patients who died developed meningitis while under therapy for miliary tuberculosis. The roentgenographic evidence of miliary tuberculosis of the lungs had, however, disappeared in each of these patients before death. Both patients had normal spinal fluid before treatment of miliary tuberculosis was instituted. The course of the meningitis in these two patients was not significantly different from that observed in other patients with meningitis at the time treatment was begun. Patient 1 showed apparent improvement in the meningeal infection, although he presented evidence of progressive hydrocephalus when therapy was discontinued. Relapse appeared 70 days after the ces-

* Supplied by Dr. William Tillett of New York University College of Medicine.

TABLE 2

TABLE 2

MILIARY TUBERCULOSIS

Case	Age	Race	Sex	Other TB at start of Rx	Treatment			Remarks	Results
					Days	S'M (gm.)	Other		
1	3-4/12	N	M	None	72	45.5	0	Miliary arrested by 72nd day.	
					97	97.0	0	Meningitis developed on 72nd day but apparently arrested by 169th day. Received 61 I.T. injections totaling 1.53 gm. S'M.	
					0	0	0	Relapse of meningitis on 238th day. Hydrocephalus present. Not retreated.	Died on 268th day.
2	5-11/12	W	F	Primary Possible CNS				Received S'M beginning 204 days earlier, totaling 56 gm. over 54 days for suspected tuberculous meningitis.	
					77	38.5	Diasone®	Miliary apparently arrested by 77th day. Organisms sensitive to S'M.	
					42	26.0	PASA Promizole®	Relapse of miliary 181 days after 1st attack. Organism sensitive to S'M.	In good condition 24 mo. after 1st attack of miliary tuberculosis.
3	2- 6/12	W	F	Primary	90	90	0	Developed tuberculous tenosynovitis 12 mo. after onset. S'M resumed.	Miliary arrested 17 mo. after start of Rx.
4*	1- 8/12	N	F	Primary	99	17.4	Promizole®	Developed tuberculous osteomyelitis of astragulus 13 mo. after onset. S'M resumed.	Condition good. Miliary and osteomyelitis arrested 25 mo. after start of Rx.
5	5/12	N	F	Primary	42	25.2	PASA Promizole®	Meningitis developed 52nd day.	
					70	44.1	PASA Promizole®	Miliary apparently arrested. Hydrocephalus present.	Died on 132nd day.
6	7	N	F	Calcified Primary T.B. hip	84	205.8	PASA	Progressive improvement.	Good condition. Miliary arrested 13 mo. after start of Rx.
7	9/12	W	M	Primary	69	62.1	PASA	In 3rd mo. of treatment at present.	Condition good but under Rx.

* See Figs. 1A, B and C.

sation of therapy. The clinical severity and an existing hydrocephalus seemed to preclude further treatment. Patient 5 had evidence of progressive deterioration from the time the diagnosis of meningitis was established and she died 80 days later with a tremendous hydrocephalus readily apparent by clinical and postmortem examination.

The five remaining patients with miliary tuberculosis are known to be alive from 3 to 25 months from the start of treatment. Patients 6 and 7 have shown continuous improvement. Patient 2, who received 56 gm. of streptomycin over a course of 54 days

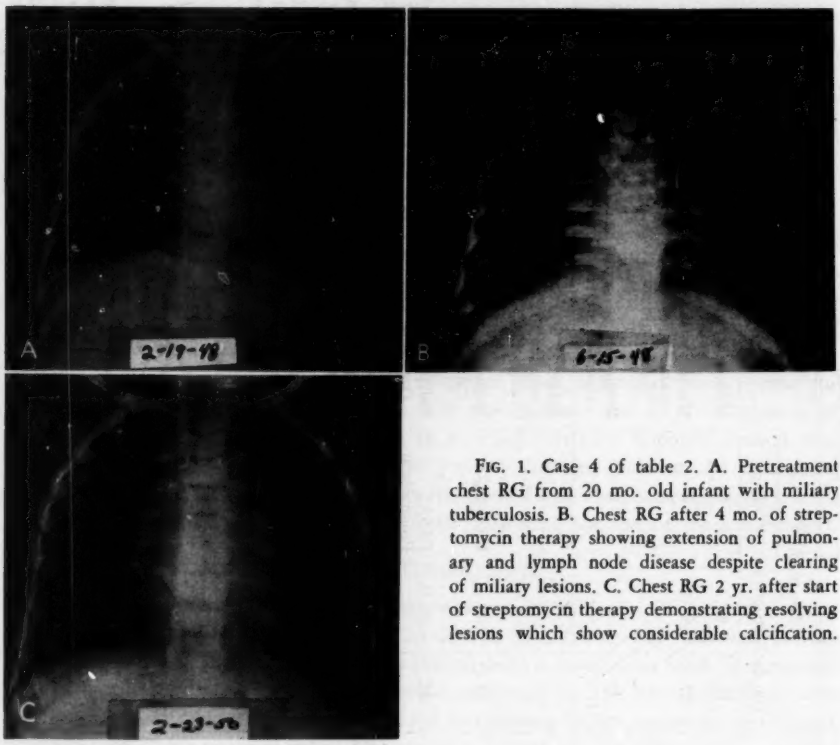

FIG. 1. Case 4 of table 2. A. Pretreatment chest RG from 20 mo. old infant with miliary tuberculosis. B. Chest RG after 4 mo. of streptomycin therapy showing extension of pulmonary and lymph node disease despite clearing of miliary lesions. C. Chest RG 2 yr. after start of streptomycin therapy demonstrating resolving lesions which show considerable calcification.

beginning 204 days prior to the first attack of miliary tuberculosis, deserves special comment. The first attack of miliary tuberculosis was apparently arrested after 77 days of treatment but a relapse was noted 104 days later. The second attack responded promptly to treatment. The other two patients with miliary tuberculosis developed tuberculous lesions of the bones or joints approximately one year after the miliary disease was diagnosed.

The daily dose of streptomycin was 55 mg./kg. in Case 2, 100 mg./kg. in Case 5. In the patients who survived, the daily dose of streyptomycin varied from 20 mg./kg. to 100 mg./kg. No unusual reactions were noted to doses in these ranges, although the common toxic manifestation of vertigo, skin eruptions, eosinophilia and cylinduria were observed. Patients treated with the early commercial preparations of streptomycin were

apt to show considerable reaction locally at the sites of injection, but planned rotation of injection sites reduced the frequency of such reactions.

Roentgenograms of the chest showed marked improvement in 6 to 12 weeks after streptomycin therapy was instituted.

Miscellaneous Tuberculous Lesions

Experience with pulmonary tuberculosis, other than miliary types, has been limited. Eight patients, six of whom were two years old or younger, have been treated with streptomycin. All had contact with infected adults within their households (table 3). Improvement apparently has not been accelerated.

Six patients, five infants and one child with lobar tuberculous consolidations were treated with streptomycin. In only one instance, Case 3, was there significant improvement. The remaining patients were observed up to 12 months from the start of therapy. In none of these five patients was marked improvement noted either in symptoms or in roentgenographic changes. Spontaneous improvement would not have been considered unusual in each of the six patients who received streptomycin. Local or remote dissemination of tuberculosis has not, however, occurred in these patients.

One infant with endobronchial and hilar lymph node tuberculosis showed prompt improvement in the endobronchial lesions although the hilar lymph node lesions were apparently unaffected.

The remaining patient, a 12 year old girl, had rather extensive tuberculosis of the left upper lobe and probable renal tuberculosis. At the time therapy was begun, the presence of tuberculous meningitis was suspected, but this was later disproved. Significant improvement was noted in symptoms, roentgenographic findings and urinalyses. This patient also received para-amino-salicylic acid.

The daily dose of streptomycin varied from 20 mg./kg. to 75 mg./kg. The drug was administered at intervals of six hours in Patient 1 and at intervals of 12 hours in the remaining patients. The doses for most patients were approximately 25 mg./kg./day. No significant toxic reactions were noted in any patient.

In addition to the patients just noted, the pulmonary lesions in patients with meningeal or miliary tuberculosis (tables 1 and 2) have been reviewed. Roentgenographic changes indicative of improvement were apparently not accelerated by the relatively large doses of streptomycin administered for miliary or meningeal tuberculosis. For example, Case 4 (table 1) was treated for meningeal tuberculosis with 583 gm. of streptomycin over a period of 316 days. The associated hilar lymph node tuberculosis has shown essentially no change during 23 months of observation in spite of the tremendous amount of streptomycin the child received.

In general, there has been little or no acceleration of healing noted in patients with pulmonary tuberculosis. There has, however, been no evidence of spread of tuberculosis in these patients.

Three patients with tuberculous osteomyelitis of the vertebrae were treated with streptomycin. One patient, an infant, received streptomycin 250 mg. daily for eight weeks, and each of two children received streptomycin 1 gm. daily for 93 and 95 days. No significant improvement was noted in the bone lesions of these patients. One of the children, however, also had several urine cultures positive for M. tuberculosis prior to therapy whereas no positive urine cultures were obtained following the cessation of

therapy. One of the patients treated for tuberculous meningitis, Case 13 (table 1) also had tuberculous osteomyelitis. No improvement was noted in the bone lesions of this patient during therapy for meningitis.

Three children with chronic tuberculous lymphadenitis and draining cutaneous sinuses were treated with streptomycin for approximately two weeks before and two weeks after surgical excision of these infected lymph nodes. Prompt healing was noted in each patient although excision of tuberculous lymph nodes was difficult and in every instance actual or suspected wound contamination occurred. Gross and microscopic examination of the

TABLE 3

PULMONARY TUBERCULOSIS

Case	TBN	Gastric	RG	Treatment		Remarks
				Days	Gm.	
1. DC 1-3/12 WM	+	+	Rt. middle lobe consolidation.	93	46.5	Unchanged
2. WD 7-0/12 NM	+	+ (Smear)	Lt. upper lobe consolidation.	31	18.6	Unchanged
3.*SC 2-0/12 NM	+	+	Rt. middle lobe consolidation. Suspicious miliary.	29	12.8	Symptomatic improvement. Roentgenographic improvement. No miliary spread developed.
4.†GS 7/12 NF	+	+	Rt. middle lobe consolidation.	28	5.6	Symptomatically improved. RGs unchanged.
5. GB 12-8/12 WF	+	+	Lt. apex with probable cavity. Abnormal pyelograms.	42	126‡	Erroneously treated as meningitis. No apparent toxic effects from large doses of S'M. including 23 IT injections of 50 mg. of S'M. Pulmonary T.B. improved. Renal T.B. improved.
6. RS 1-2/12 WM	+	0	Emphysema. Lymph nodes.	35	9.5	Endobronchial lesions. Cleared on treatment. Lymph nodes unchanged.
7. EF 7/12 NF	+	0	Rt. upper lobe consolidation.	28	4.2	Unchanged
8. PQ 1-4/12 WF	+	0	Rt. lower lobe consolidation.	28	11.2	Unchanged

* See Figs. 2A, B and C.
† See Figs. 3A and B.
‡ Also received para-amino-salicylic acid.

excised lymph nodes revealed tuberculous lesions in each instance. To date, no relapses have been noted although no patient has been observed longer than seven months. That streptomycin is responsible for these results is not established. It is well known that surgical excision of tuberculous lymph nodes has been successfully accomplished without the concurrent administration of streptomycin.

In addition to the patients just noted, an infant with chronic tuberculous otitis media, established by recovery of M. tuberculosis by smear and culture, developed extensive lymphadenitis in the regional lymphatic tissues. The adenitis did not respond to adequate

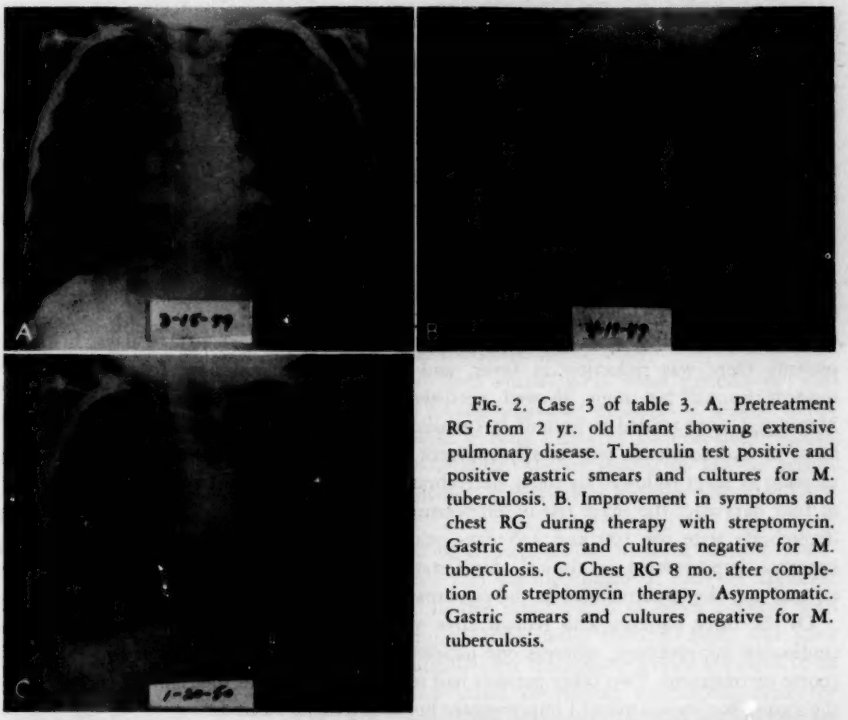

FIG. 2. Case 3 of table 3. A. Pretreatment RG from 2 yr. old infant showing extensive pulmonary disease. Tuberculin test positive and positive gastric smears and cultures for M. tuberculosis. B. Improvement in symptoms and chest RG during therapy with streptomycin. Gastric smears and cultures negative for M. tuberculosis. C. Chest RG 8 mo. after completion of streptomycin therapy. Asymptomatic. Gastric smears and cultures negative for M. tuberculosis.

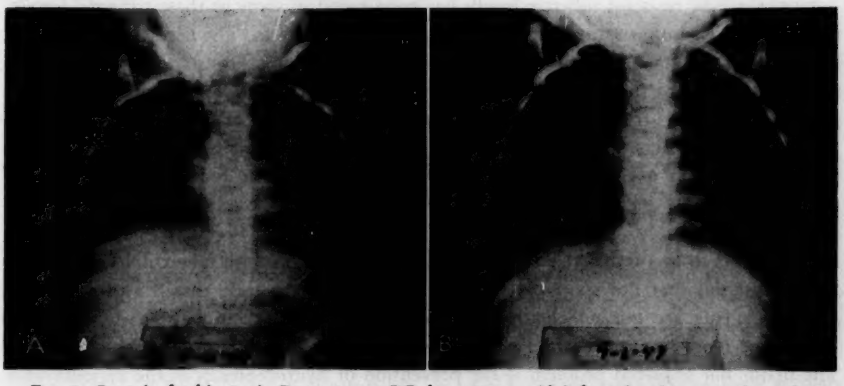

FIG. 3. Case 4 of table 3. A. Pretreatment RG from 7 mo. old infant showing extensive primary lesion. Tuberculin test positive and positive gastric cultures for M. tuberculosis. B. Post-treatment chest RG showing no significant change. Gastric culture still positive for M. tuberculosis.

doses of sulfadiazine administered orally for 14 days, but subsided promptly when streptomycin was administered. Moreover, the chronic suppurative otitis media healed. Several patients with miliary or meningeal tuberculosis have shown similar prompt regression of nonfluctuant lymph node lesions.

Discussion

The clinical course of tuberculous meningitis has been altered by the administration of streptomycin along with other tuberculostatic agents. The duration of life in many patients has been prolonged but the number of complete recoveries is indeed small. The present series of cases shows approximately the same number of survivors as do other reports of patients from whom cerebrospinal fluid M. tuberculosis was isolated by culture.[19–21]

The clinical course in these patients was rather variable. Seven patients, whose condition was considered poor or moribund when therapy was instituted, lived only 3 to 9 days from the start of treatment. Antibacterial treatment had no influence on the progress of the meningitis.

Eight patients died after periods of treatment varying from 38 to 214 days. In these patients there was reduction in fever, and their cerebrospinal fluid tended to return towards normal but none showed persistent improvement in clinical manifestations. Meningeal signs tended to become less marked, but rarely disappeared. Gradual development of hydrocephalus was usually apparent before death. Terminal events were sudden increase in fever followed by coma, decerebrate rigidity, convulsions and death within two to four days after the sharp rise in temperature. Two patients in this group remained in a decerebrate state for 109 and 135 days, respectively, during which time there was no apparent improvement in clinical manifestations, although the temperature returned to normal and the abnormalities in the cerebrospinal fluid were reduced.

Of the three patients who remain alive after therapy was discontinued, two showed continuous improvement, whereas one patient had a relapse which responded to a second course of treatment. Two other patients had relapses. One patient died during the relapse; the second has shown marked improvement but is still being treated.

Emergence of resistant tubercle bacilli has been noted in some of these patients despite the concurrent administration of agents other than streptomycin. The necessity to continue therapy over a long period of time favors the development of resistant organisms. The fact that tubercle bacilli were cultured from the cerebrospinal fluid of all but three of the 22 patients suggests that these patients harbored large numbers of bacteria. In a bacterial population of great size, a relatively larger number of resistant bacilli are likely to be present. Although it cannot be established, it seems reasonable to assume that patients in whom tubercle bacilli are isolated with ease from the cerebrospinal fluid should respond less favorably.

The results in this series of unselected, consecutive patients with tuberculous meningitis are encouraging but not spectacular. It seems reasonable to state that the present antibacterial agents are not sufficiently active to produce rapid clearing of the meningitis. Hence, the more severely affected patients are apt to die shortly after treatment is begun. The major but unsolved problem is the prevention of hydrocephalus in the patients who survive long periods of treatment. For many of these patients the use of the streptococcal enzymes, streptokinase and streptodornase, prepared according to the method of Christensen[25] and used as described by Tillett and Sherry[26, 27] and by Cathie,[28] may offer some hope. These enzymes cause the solution of tuberculous exudates. Their use in chronic tuberculous meningitis is recent and their efficacy is under investigation. Theoretically, at least, some benefit may be obtained from their use since many patients with chronic meningitis develop obstruction to the flow of cerebrospinal fluid solely from the precipita-

tion of tuberculous exudates over the various channels of cerebrospinal fluid circulation. Obstructions to cerebrospinal fluid circulation may, on the other hand, be produced by the localization of a tuberculoma adjacent to the ventricular systems. If the tuberculoma enlarges, partial or complete obstruction occurs. Since the distribution of tuberculomas within the substance of the brain cannot be controlled, it is inevitable that some patients will develop hydrocephalus from mechanical obstruction to the flow of cerebrospinal fluid.

Although the present therapy of tuberculous meningitis is only partially successful, it would seem justifiable to treat all patients with this infection. In some patients the infection seems to be arrested, although recurrence after long periods of apparent recovery has been reported.[29] It is difficult to recommend a definite plan of therapy other than the prolonged administration of streptomycin in large doses intramuscularly along with the intrathecal administration of the same agent. Present information indicates that some agent such as PAS or promizole® should be administered concurrently.

The treatment of miliary tuberculosis has been encouraging. Most patients do well providing meningitis does not develop. The roentgenographic evidence of miliary tuberculosis of the lungs disappears in 6 to 12 weeks in most instances. Clinical improvement is usually readily apparent within the same interval. Miliary lesions of various organs were difficult to demonstrate by gross examination at autopsy in patients who died from meningitis after long periods of treatment. Tissue sections from various organs, and especially the lungs, showed partially healed or atypical lesions in these patients. However, it is not presumed that all tuberculous foci are eliminated in spite of apparent clinical and roentgenographic improvement. In this small group of seven patients with miliary tuberculosis, two developed meningitis while under therapy. Bone and joint tuberculosis became apparent in two other patients after the miliary lesions appeared to be arrested. One additional child had a second attack of miliary tuberculosis after the apparently successful control of the first attack. Thus, although the small miliary foci are controlled and may heal completely, it is obvious that other foci remain which may become clinically significant after various intervals of time.

It would seem that a long period of treatment with relatively high doses of streptomycin in combination with an adjuvant drug is indicated. Prolonged observation is necessary after therapy is discontinued since other foci of tuberculosis may become manifest at any time. Should such occur, treatment with streptomycin may be resumed.

The value of streptomycin and other agents in the treatment of various forms of tuberculosis other than miliary or meningeal tuberculosis is extremely difficult to determine. There is suggestive evidence in this and other reports[17, 24] that surgical procedures can be carried out more safely when streptomycin is administered.

Primary pulmonary lesions, especially in children, generally have a good prognosis. It seems reasonable to treat such patients expectantly, reserving the use of streptomycin for those patients who develop progressive lesions. Since progression of the disease may often be halted by the use of streptomycin, it would appear justifiable to treat patients with such lesions with short courses of streptomycin. It is suggested that such patients receive streptomycin, or dihydrostreptomycin, in doses of 20 to 30 mg./kg./day, in one or two doses, for periods of 28 days. Such a program should prevent the development of streptomycin-resistant tubercle bacilli, and should reduce serious toxic effects of streptomycin.

Small pulmonary lesions, which as a rule retrogress spontaneously, should be treated conservatively.

There are insufficient data on which to evaluate the usefulness of streptomycin and other agents on tuberculous lesions other than meningeal, miliary or pulmonary ones. It would seem advisable, if treatment with streptomycin is undertaken, to limit the treatment to courses of perhaps four weeks. The course of treatment might be repeated if necessary after a rest period of one to two weeks. Such a plan of therapy should reduce the toxic manifestations of streptomycin and also reduce the frequency with which streptomycin-resistant tubercle bacilli appear.

Summary

Streptomycin, or dihydrostreptomycin, along with other agents, such as promizole® or PAS, is of value in the treatment of serious forms of tuberculosis in infants and children. Progressive pulmonary tuberculosis and miliary tuberculosis seem to respond most satisfactorily. Tuberculous meningitis has a serious prognosis but some patients apparently have this infection arrested.

The use of streptomycin for patients with forms of tuberculosis which have a good prognosis without treatment is not recommended. The potential toxicity of the drug and the possible emergence of streptomycin-resistant tubercle bacilli are the major reasons for this recommendation.

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SPANISH ABSTRACT

El Tratamiento de la Tuberculosis en Infantes y Niños

El uso de la estreptomicina o de la dehidro-estreptomicina, combinada con otros agentes como Promizole (R) y PAS, es de gran valor terapeútico en las formas severas de tuberculosis infantil. Se señala que las formas de tuberculosis pulmonar progresiva y de tuberculosis miliar responden satisfactoriamente al tratamiento. El pronóstico de la meningitis tuberculosa sigue siendo grave, pero en algunos pacientes esta infección ha sido aparentemente detenida.

El autor no recomienda el uso de la estreptomicina en pacientes padeciendo de tipos de tuberculosis de pronóstico favorable. Esta recomendación se basa principalmente en la toxicidad potencial de la droga y en el posible desarrollo de una resistencia del bacilo tuberculoso a la acción de la estreptomicina.

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BROCK PROCEDURE FOR THE RELIEF OF PULMONARY STENOSIS IN THE TETRALOGY OF FALLOT

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PULMONARY stenosis may exist as a single defect or may be present in combination with other defects such as overriding of the aorta, interauricular or interventricular communications, patent ductus arteriosus, and the like. The stenosis may be valvular or infundibular, or both. If the stenosis is purely valvular, the outflow tract of the right ventricle is normal; the pulmonary artery may be hypoplastic, normal or dilated. If there is infundibular stenosis, the outflow tract of the right ventricle is interrupted by a ridge of tissue, in effect a defective septum which encroaches upon its lumen and contributes to the formation of a fifth cardiac chamber. This chamber may be so small as to be inappreciable when the ridge of tissue is immediately subvalvular, or it may be quite large when the septum is lower in the ventricle. As in the case of valvular stenosis, the pulmonary artery may be hypoplastic, normal or dilated. Whatever the type of defect the ultimate effect is the same; blood cannot pass with ease into the pulmonary circuit (see Fig. 1)..

Brock[1] in 1948 reported a new type of operation for the relief of congenital pulmonary stenosis. He reasoned that while shunting procedures had their advantages it would be far better surgically and physiologically to directly attack the stenotic valve, or the infundibular obstruction, than to merely by-pass it. Doyen[2] had attempted direct division of what was thought to be a stenosed pulmonary valve in 1913. Thereafter, there had been no further attempts until that of Brock. Originally he tried to approach the valve thru the left pulmonary artery, first observing the anatomic situation through a cardioscope. However, this proved to be unsatisfactory from the point of view of patient and surgeon. Therefore, the remaining avenue through the right ventricle was employed, just as Doyen had used it years earlier.

Inasmuch as pulmonary stenosis may be either infundibular or valvular, two procedures were devised. For the correction of valvular stenosis an incision is made through the right ventricular wall, a short distance proximal to the valve. A probe may first be passed through the incision and into the pulmonary artery to gauge the degree of stenosis. A special diamond-shaped knife with sharp leading edges and noncutting olivary tip (see Fig. 2a) is then inserted and guided to the region of the valve where the tip engages in the contracted orifice. This valvulotome is then pushed through the valve into the pulmonary artery, cutting across the lateral aspects of the valve (see Fig. 3b). It is withdrawn and a dilating sound is inserted to widely separate the two cusps which have been formed by the knife. The ventricular incision is then closed. For cases of infundibular stenosis,

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Brock advises an incision into the ventricular chamber proximal or distal to the obstructing tissue. A collar of this tissue is then excised by means of a cutting punch (see Fig. 2b), thus greatly enlarging the diameter of the channel (see Fig. 3a).

Brock's first report[1] concerned three patients, all of whom were benefited by operation. At the time of his second report[3] he had added two additional cases; since then he has operated upon a number both here and in England with excellent results. Recently Blalock,[4] in an address before the American Surgical Association, reported a series of 19 cases of Brock valvulotomy for "pure" pulmonary stenosis with excellent results. A num-

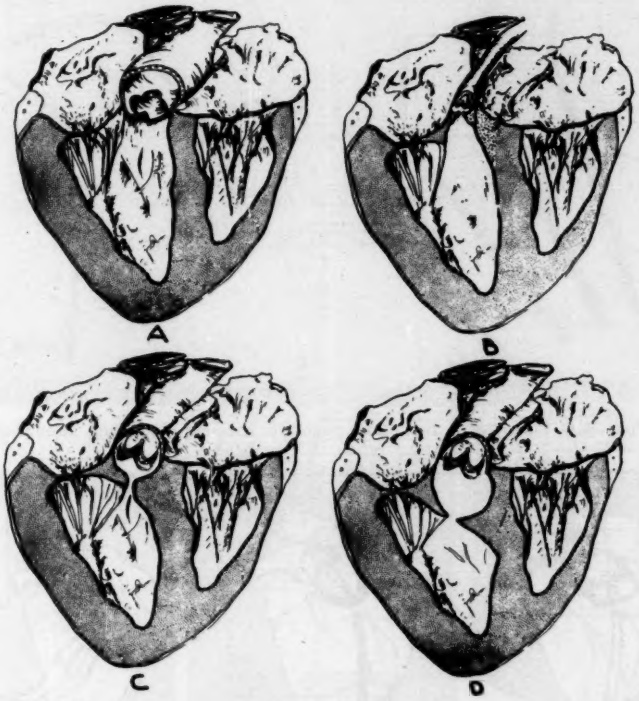

FIG. 1. Types of pulmonary stenosis. A. Valvular stenosis. Conical valve. Dilated pulmonary artery. B. Hypoplastic pulmonary artery with infundibulum stenosis in immediate subvalvular region. C and D. Variations in extent of size of infundibulum chamber.

ber of these had been performed by Brock himself while at Johns Hopkins Hospital. During the discussion which followed his paper, he stated that the shunt operations were preferable in cases of typical tetralogy of Fallot, partly because of the presumed rarity of valvular stenosis in this condition and partly because of the technical difficulties associated with removal of the much commoner obstructing infundibular septum. The present investigators' experience in the following cases is somewhat at variance both in regard to the incidence of valvular stenosis and the difficulty of overcoming infundibular stenosis. These direct approach procedures have now been used in eight cases of tetralogy of Fallot. The authors were forced to modify the attack on the infundibular septum but

otherwise have followed Brock's technic. In four cases of infundibular stenosis operated upon to date, the incision in each instance was made immediately upon the septum, making the use of the Brock punch impossible. In the first of these (Case 5) the condition of the patient was so critical that nothing could be done except to quickly and forcibly en-

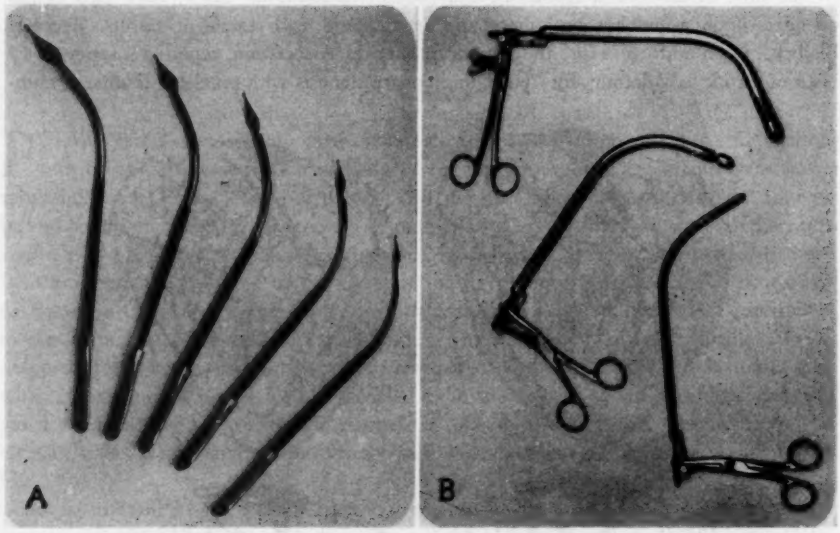

FIG. 2. A. Pulmonary valvulotome. B. Cutting punch for excising obstructing infundibulum tissue.

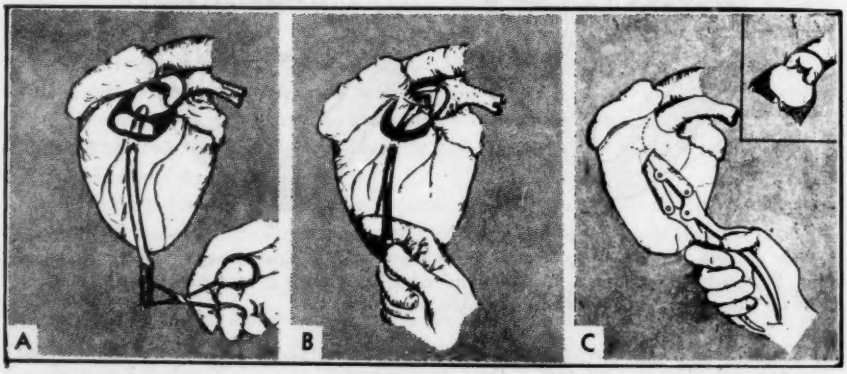

FIG. 3. A Cutting punch for excising obstructing infundibulum tissue. B. Valvulotome in use. C. Rongeur for removal of obstructing infundibulum tissue.

large the channel digitally and by instrumentation, and terminate the procedure. As a result of this experience, one of the authors (R. P. G.), when confronted with the same problem a few days later, was prepared with a small sharp bone rongeur with which he was able to remove a segment of tissue through the opening in the myocardium. This led to the development of a special ronguer with tapering jaws, of a shape that permits easy

insertion through the myocardial incision with good hemostasis and engagement upon the obstructing tissue for removal of a wedge-shaped section (see Fig. 3c).

Case Reports

Case 1. M. B., female, aged 3½ yr. Tetralogy of Fallot with valvular stenosis. Diagnosis by angiocardiography. Severe cyanosis and greatly diminished exercise tolerance. When at operation

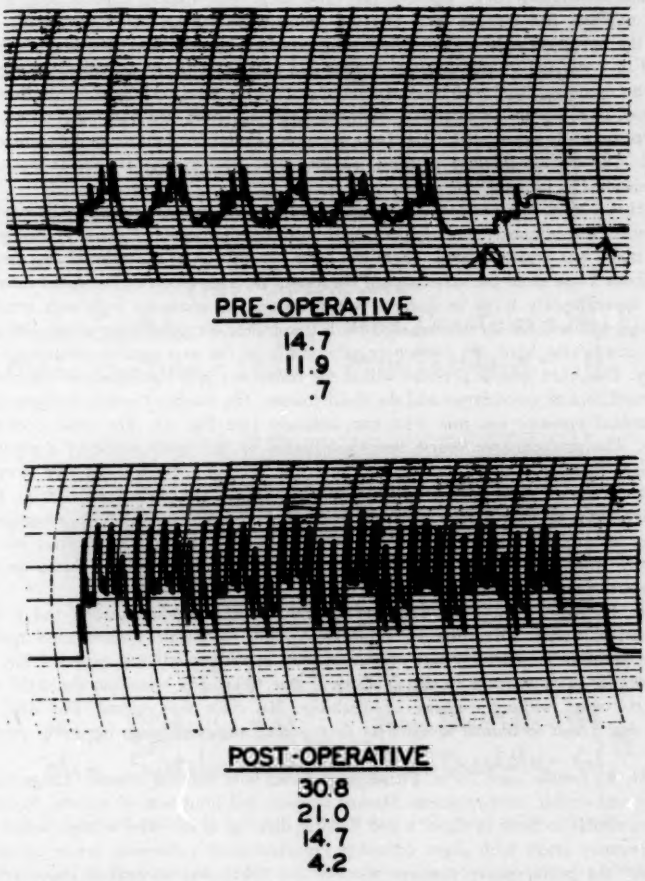

Fig. 4. Direct tracing of pre- and postoperative pulmonary artery pressure.

the pericardium was opened the pulmonary artery was found to be a dilated fusiform structure arising from the ventricle in normal position. It was constricted in the region of the valve, being about 1.5 cm. in diameter at that point and 3.0 cm. in diameter distally. A fine thrill could be felt in the artery which was not felt over the heart. Intraluminal mean systolic pressure was 14.7 mm. mercury (Lilly Manometer). Two stay sutures were placed in the myocardium about 3 cm. proximal to the pulmonary valve and a 1.5 cm. incision made between them. By traction on the sutures bleeding from the incision was controlled completely. The smallest of a standard set of urethral sounds was now passed through the incision and guided into the pulmonary artery. It fitted rather snugly at the

level of the valve. The sound was removed and the medium sized Brock knife (12 mm.) was inserted. It met slight resistance at the valve but slipped through into the artery with no difficulty. Immediately the artery which had been soft and easily compressed became distended and firm. The knife was withdrawn and a number 30 urethral sound could now be passed through the divided valve without particular resistance. It was removed and the opening in the myocardium was closed with 3 interrupted sutures. The pressure in the pulmonary artery was now 30.8 mm. mercury (see Fig. 4). During the procedure little blood was lost. It was noted by the anesthesiologist and other observers that immediately upon opening the valve there was marked improvement in the child's color. The nailbeds had become pink and the generalized cyanosis had disappeared. Upon completion of the operation only a faint bluish tinge remained in the lips. She was discharged from the hospital in 1 wk. and by that time could walk and play about the ward without apparent distress. There was no cyanosis; RBC had fallen from a preoperative level of 8.0 to 5.0 million/cmm. and the Hgb. from 19 to 15 gm./100 cc. The electrocardiogram showed less right heart strain. Six months later she was normally active; there had been no cyanosis, and on fluoroscopy her cardiac silhouette was normal. The systolic murmur in the third interspace near the sternal border was still present but had diminished in intensity.

Case 2. H. C., male, aged 12½ yr. Tetralogy of Fallot with valvular stenosis. Diagnosis by angiocardiography. Severe cyanosis and dyspnea with marked limitation of activity. At operation the pulmonary artery was greatly dilated. There was some constriction at the point of exit from the right ventricle. About 2 cm. from the valve area in the antero-superior aspect of the vessel there was noted an area of approximately 1 cm. in diameter which bulged out markedly with each systolic contraction. Over this area was felt most intensely a thrill transmitted throughout the artery. On invaginating this portion toward the heart the pulmonary valve could be felt as a conical prominence at the base of the artery. The mean systolic pressure within the vessel was 23.8 mm. mercury. Upon dividing the valve the vessel became much firmer and the thrill coarser. The localized systolic bulging disappeared. The intraluminal pressure was now 33.6 mm. mercury (see Fig. 5). The child's color improved immediately. The postoperative course was complicated by the development of a pleural effusion which required thoracentesis. He was discharged on the 17th postoperative day free of cyanosis. His erythrocyte and hemoglobin levels had fallen from 5.5 million/cmm. and 16 gm./100 cc., respectively, to 4.0 million/cmm. and 10 gm./100 cc. Three months postoperatively he was engaging in sports and showing no evidence of cardiac disability. On fluoroscopy his pulmonary conus was prominent but the cardiac silhouette was in other respects normal. There had been no change in the systolic murmur present in the third interspace.

Case 3. R. B., male, aged 7 yr. Tetralogy of Fallot with valvular stenosis and a large interventricular septal defect. Diagnosis by angiocardiography. Moderate cyanosis and rather marked limitation of activity. Valvulotomy was performed with immediate relief of cyanosis. The pulmonary artery was similar in appearance to that of Case 2. One week after operation the child was able to play about the ward without evidence of disability. His color was normal. His RBC count and hemoglobin had fallen to normal levels. His short course since discharge has been uneventful and satisfactory.

Case 4. M. R., female, aged 18 yr. Tetralogy of Fallot with valvular stenosis. Diagnosis by angiocardiography and cardiac catheterization. Marked cyanosis and limitation of activity. At operation the findings were similar to those of Cases 2 and 3. After division of the valve a large sound was passed into the pulmonary artery with slight difficulty. Prevalvulotomy pulmonary artery pressure was 28 cm. of water; the postoperative pressure was 48 cm. There was immediate improvement in the cyanosis; her lips and nailbeds became pink. Her postoperative course was complicated first by the development of pleural effusion which required thoracentesis. She was thought to be improving when a short, soft pulmonic diastolic murmur developed and on fluoroscopy the right ventricle was found to be increasing in size. Ambulation was allowed for a few days during the second week after operation but signs of right heart failure developed. In spite of strict bed rest the signs of failure persisted and those of pulmonary insufficiency increased. Classical signs of tricuspid insufficiency developed. Because it was apparent that the pulmonary valve had been opened too widely and that her death could be expected shortly, another operation was performed during which the wall of the pulmonary artery was plicated near its origin in an attempt to narrow the opening in the region of the valve. Pulmonary artery pressure following this procedure was 30 mm. of water. A severe transfusion

reaction occurred postoperatively, and after a stormy course of 10 days the patient died. Details of the case will be presented in another communication.

Case 5. K. K., male, aged 3 yr. Tetralogy of Fallot with infundibular stenosis, marked cyanosis and limitation of activity. At operation the myocardial incision was made over and partially into the infundibular septum. The child's condition deteriorated rapidly. Because it was apparent that unless a pulmonary flow superior to that existing preoperatively could be induced the child would not survive, a finger was inserted into the incision and the tiny septal aperture dilated as much as possible. The myocardium was then quickly sutured. Cardiac action ceased. After alternate compression and

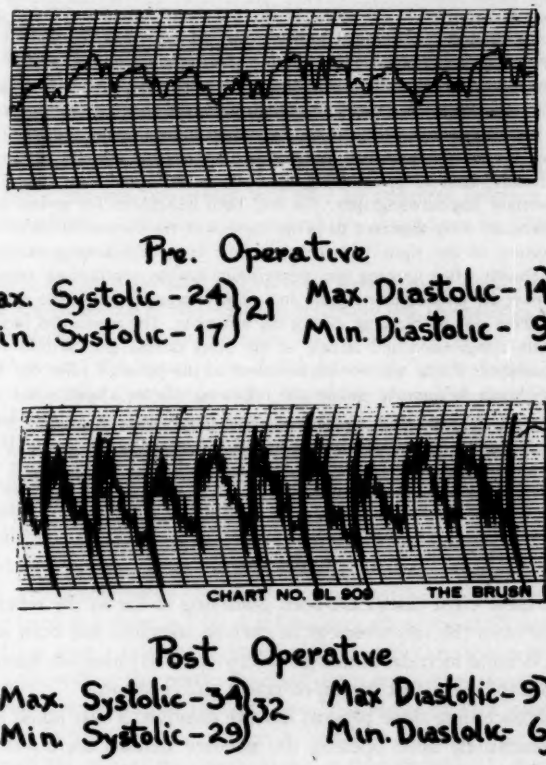
Pre. Operative
Max. Systolic - 24 } 21
Min. Systolic - 17 }
Max. Diastolic - 14 } 12
Min. Diastolic - 9 }
CHART NO. BL 903
THE BRUSH
Post Operative
Max. Systolic - 34 } 32
Min. Systolic - 29 }
Max Diastolic - 9 } 8
Min. Diastolic - 6 }

FIG. 5. Direct tracing of pre- and postoperative pulmonary artery pressure.

release of the heart had been carried out for several minutes a spontaneous beat was re-established and the chest closed. The postoperative course was stormy. The child seemed as cyanotic as before operation. Attacks of severe paroxysmal dyspnea were frequent and there was evidence of right heart failure. After 1 wk. there was improvement and at the end of 3 wk. the child was in condition to be discharged. He was not as cyanotic as on admission and was able to play about the ward in a normal manner. Four months postoperatively it was found that the improvement had continued and his exercise tolerance had now approached that of a normal child.

Case 6. D. J., female, aged 4 yr. Tetralogy of Fallot with infundibular stenosis, marked cyanosis and limitation of activity. At operation the myocardial incision was again made upon the infundibular septum. A small bone rongeur was inserted into the incision and a portion of the septum removed. Because the rongeur did not properly tamponade the myocardial opening, excessive hemorrhage

occurred. Cardiac contractions ceased but were restored by rapid transfusion and cardiac massage following closure of the myocardial incision. Before leaving the operating room the child was pink. Postoperatively there was tachycardia for several days. One week after operation, while ambulatory, signs of right heart failure appeared. Digitalis and bed rest brought about improvement within a few days. She was discharged on a daily maintenance dose of digitalis and this was continued for 6 wk. Three months after cessation of therapy she was without cyanosis and her exercise tolerance was thought by observers to be normal.

Case 7. L. F., male, aged 3 yr. Tetralogy of Fallot with infundibular stenosis. Diagnosis by angiocardiography. Marked cyanosis and limitation of activity. Condition poor. At operation there was a thrill which was strongest at the origin of the pulmonary artery and faded out distally. The artery was moderately dilated. Intraluminal pressure was 25 cm. of water. Partial septectomy was performed and the pressure rose to 31.5 cm. Cyanosis disappeared almost wholly within the next few minutes. Ambulation was allowed on the 5th postoperative day. After 2 days, however, signs of right heart failure developed. Bed rest and digitalis brought about improvement and at the time of discharge there was no cyanosis. His activities have been limited by his parents to the present time but it is known that his exercise tolerance has increased appreciably over the preoperative level.

Case 8. A. S., female, aged 21 yr. Tetralogy of Fallot with infundibular stenosis. Her condition was too poor to warrant angiocardiography. She had been bed-ridden for several months. Cyanosis was marked. At operation there appeared to be no stenosis of the valve. The thrill was most intense over the distal portion of the right ventricular outflow tract, diminishing in intensity over the pulmonary artery. Shortly after opening the pericardium cardiac contractions ceased. Promptly an incision was made over the infundibular septum and a fairly large portion of the septum was removed with the rongeur. There was no bleeding during the maneuver. The myocardial incision was quickly sutured and alternate compression and release of the heart carried out. Within 10 sec. a normal rhythm was re-established. There was no improvement in the patient's color for about 3 hr. after operation. She then began to improve and by the following day the cyanosis had in large measure disappeared. Because of the experience in previous cases ambulation was delayed for 2 wk. She was discharged shortly thereafter with instructions to limit her activities for 1 mo. However, she disregarded the advice, cramming her days with the experiences she had missed during her previous life. When last seen, almost three months postoperatively, there was minimal cyanosis of the nailbeds, cardiac size had not increased and she was able to carry on normal activities.

Comment

The results in these eight cases have been gratifying so far as the relief of cyanosis is concerned. In six cases the improvement in exercise tolerance has been striking; in one there has been a definite increase. Although follow-up observation has been of short duration there is reason to believe that the improvement will continue.

Several points concerning these patients deserve mention. It was noted in all cases save 5 and 8 that immediately upon opening the stenosed channel there was great relief of cyanosis. In Case 5 the operation was a makeshift affair and little was expected from it. In Case 8 the patient's condition was very poor and cardiac arrest occurred prior to manipulating the heart; it was not until some time after operation that the desired improvement in color developed. This immediate change in color is striking. It is remarkable to see the dark blue giving way to an almost normal pink in the space of a few heart beats. There has been nothing comparable in the cases of shunt procedures done by the authors. However, it is worthy of note that Brock's original cases were cyanotic for some time postoperatively and the development of normal coloration was a gradual process.

Five of the patients developed postoperative complications. The convalescence in Case 2 was prolonged because of the development of a sterile pleural effusion which required thoracentesis. This cannot be regarded as a complication of the particular procedure, however, as it might occur in thoracotomy performed for any purpose. The fact that the

pericardium is not closed tightly in this operation permits leakage of pericardial fluid into the pleural space, thus adding to the collection.

In four cases right heart failure developed. In Cases 5, 6 and 7 there was considerable trauma to the myocardium incident to removing the impediment in the infundibulum. The electrocardiogram immediately postoperatively and for at least one week in all these cases indicated a degree of myocardial ischemia. It is felt that in Cases 6 and 7 too early ambulation was a factor in the production of failure. In Case 5 there was no reason to suspect that the child would survive operation. His postoperative course was marked by disturbances in rhythm and failure. It is interesting that his improvement has been progressive. Evidently the stenosed channel was dilated sufficiently to increase pulmonary flow to an appreciable degree and has not contracted again. In Case 4 the failure was due to pulmonary regurgitation of a degree for which compensation was impossible. It is apparent that the valve was opened too widely or that the dilatation consequent upon the valvulotomy tore the cusps so that they could not close competently. The surgeon must be cautious in his choice of knife and use one which will give an adequate aperture without inviting regurgitation. In addition, the incised valve probably should not be dilated afterward for fear of tearing the margins.

The fact that 4 of the 8 patients had valvular stenosis is of great interest. It has been considered that the incidence of this lesion is relatively low in tetralogy of Fallot and that infundibular stenosis is practically the rule. The authors' experience in these and other cases does not bear out this assumption. Brock has made similar observations.

As can be readily appreciated it is most important, if possible, to make a preoperative diagnosis of the point of obstruction. For that reason, angiocardiography is mandatory in those patients who are candidates for operation. Only the ones whose condition is critical should be excused. Many more lives are lost because of surgery carried out in the face of an incorrect clinical diagnosis than from procedures such as angiocardiography which might make diagnosis definitive. If exact preoperative diagnosis is not possible—and sometimes angiocardiography does not aid in differentiating valvular from infundibulum stenosis—then certain observations made on the exposed heart are helpful. If the pulmonary artery is dilated and there is a localized bulging where the thrill is most intense, one is probably dealing with a valvular stenosis and the cervix-like valve cone may be palpated by invaginating the wall at this point. This bulging is due to the strong jet of blood which enters the vessel in an eccentric fashion; this eccentricity of flow may account for the marked dilatation in some cases: first there is localized dilatation due to the force of the jet; as it increases the rest of the artery dilates in compensation. If the thrill is most intense in the subvalvular region and fades out distally along the pulmonary artery, one is probably dealing with an infundibulum stenosis.

Discussion

The anastomotic procedure of Blalock and Taussig[5] was a monumental step in the treatment of cyanotic congenital heart disease. Potts, Smith and Gibson[6] made a sterling contribution with the introduction of direct pulmonary artery-aorta anastomosis, thus creating a "window" ductus arteriosus. Both of these procedures, particularly that of Blalock, have been carried out on large numbers of patients in many clinics and the results have justified the hopes born when Blalock and Taussig made their initial report. Hundreds of infants and children doomed to an early death or a desperate invalidism have been given life and comfort, and a generation of victims are grateful.

However, the objections to the shunting procedures are serious. The mere presence of an arteriovenous fistula or a patent ductus arteriosus in an individual with an otherwise normal cardiovascular apparatus is considered adequate reason for surgical correction of the lesion because of manifest or potential ill effects. Excessive cardiac work results from the inefficiency of a system including such a shunt. Cardiac reserve is lessened, leading to early limitation of activity and a tendency to cardiac failure. In addition, in cases of patent ductus arteriosus there is a predisposition to the development of subacute bacterial endocarditis. These same forces are in play in cases of congenital pulmonary stenosis treated by the production of an arteriovenous shunt. In a number of operated cases this first ill effect has been seen, particularly in patients who had a Potts anastomosis, in which the size of the communication may easily be made too large. Subacute bacterial endocarditis uncommonly develops in the first decade in cases of patent ductus arteriosus; inasmuch as shunt procedures have been performed for a relatively short time, it will be some years before the incidence of infection arising at the operative site will be appreciated. It has been suggested that in the presence of pulmonary stenosis plus a septal defect an artificial patent ductus might not have the same effect as a ductus in an otherwise normal person. However, on simple engineering principles such hypothesis would seem to be untenable. Thus, it appears that the shunt would tend to prolong life by preventing anoxemia and actual asphyxiation but it seems also probable that it in itself provides a limit to the extension of life span and augurs ill for the individual.

When one considers that, as Blalock and Taussig pointed out, the main difficulties in pulmonary stenosis, whether it be an isolated defect, a part of the tetralogy of Fallot, or with an interventricular or interauricular communication, arise from the fact that insufficient blood is able to reach the lungs for oxygenation, it is obvious that the ideal correction of this lack would be the removal of the obstruction and not the construction of an avenue to by-pass it. Experience with the surgical relief of mitral stenosis convinced the authors that removal of the impediment to blood flow is surgically and physiologically sound and preferable to the production of a shunt.[7-9] For this reason Brock's procedure must at present be considered that of choice in cases of pulmonary stenosis. It gives the individual a relatively normal pulmonary circulation without, at least theoretically, making him susceptible to the dangers just mentioned. True, a number of questions arise which are unanswerable at present. What will be the incidence and effect of pulmonary regurgitation in those cases in which the stenosed valve is divided? That it will occur in certain cases is shown by the experience with Case 4; however, it probably will rarely be of a greater degree than can be compensated for by the hypertrophied right ventricle. What danger lies in the presence of a bicuspid pulmonary valve? Undoubtedly one must consider the possibility of the development of subacute bacterial endocarditis, but its incidence in individuals with congenital bicuspid pulmonary valves is not striking. Finally, what is the probability that the valves might again fuse at some time postoperatively, or of the outflow tract again becoming obstructed in those cases in which infundibular stenosis has been corrected? Again, no definite answer can be given. However, it would seem reasonable to assume in the light of the authors' experience with some 65 cases of mitral commissurotomy that if the valves do not fuse within the immediate postoperative period, and they do not as evidenced by the continued absence of cyanosis, they will not fuse subsequently. In regard to infundibular stenosis, with Brock's technic there may be some tendency to fibrosis and contraction, but the contraction in all probability would

not be sufficient to significantly prevent an adequate pulmonary flow. With the procedure used in the authors' cases of infundibular stenosis, fibrosis and contraction, occurring in one segment of the collar of tissue, would tend to open the channel even more.

Summary

The surgical relief of pulmonary stenosis has been both direct and indirect. The indirect procedures have inherent dangers; the direct approach of Brock appears to be without these dangers and the circulation is allowed a more normal course. This approach entails an incision into the right ventricular chamber and the cutting of the stenosed pulmonary valve or the removal of obstructing tissue in the outflow tract of the right ventricle. Cyanosis is usually relieved immediately. The patient's exercise tolerance is significantly increased.

Eight cases are presented.

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Spanish Abstract

Técnica Operatoria Directa de Brock en el Tratamiento de la Estenosis Pulmonar de la Tetralogía de Fallot

Se describen las técnicas operatorias usadas en el tratamiento de la estenosis pulmonar. La técnica indirecta ofrece ciertos peligros, tales como la creación de una corriente arteriovenosa "arteriovenous shunt"; la técnica directa de Brock parece no ofrecer este peligro y además permite a la circulación pulmonar seguir su curso normal.

La técnica directa de Brock consiste en una incisión dentro del ventrículo derecho y excisión de la válvula pulmonar estenosada o excision del tejido obstructivo a la salida de la arteria pulmonar. La cianosis desaparece inmediatamente y las pruebas de tolerancia al esfuerzo físico del paciente se aproximan a las de un individuo normal.

Los autores reportan ocho casos. Se registró una defunción.

230 North Broad Street

PROTEIN-BOUND IODINE IN INFANTS FROM BIRTH TO ONE YEAR OF AGE

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THOUGH it is known that in children with obvious clinical stigmata of cretinism the serum precipitable or protein-bound iodine falls below values characteristic of adults,[1] no standards of reference are available based on apparently normal infants. This need is emphasized by the knowledge that pregnancy alters the protein-bound iodine as well as the circulating thyroxin in the mother.[2-4] The data herein presented indicate that during the first year of life, and particularly during the initial weeks, the protein-bound iodine values are clearly higher than those present in older subjects.

PBI
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MATERIALS AND METHODS

One hundred fifty-four sera from a series of 110 infants ranging up to 1 yr. in age have been analyzed in duplicate for protein-bound iodine concentrations by the method of Barker, modified.[5, 6] The subjects were selected at random from the nursery of the Elizabeth Steel Magee Hospital or from well-baby clinics.* In a limited number of samples thyroxin levels have been determined as well.[5, 7] All the infants had been born at term following an uncomplicated pregnancy. The history and examination, including measurements of body weight, crown-rump length, etc., indicated that they were in good health and developing normally.[8] The results are presented in 1 chart and 2 tables.

RESULTS

A. Findings During the Neonatal Period: In chart 1 it may be seen that the protein-bound iodine of the infant is usually at its highest during the first week of life, ranging up to 15.4 gamma per cent. In table 1 it is further evident that values obtained in the course of the 12 hours following birth are statistically indistinguishable from the elevated concentrations observed in a group of pregnant women, about one quarter of which consisted of mothers of babies herein described.[4] On the other hand, levels recorded during the remainder of the first week, at the end of any one of three time intervals, are significantly higher than those which prevail immediately following birth (lines 2, 3, and 4 in table 1).

Fractionation studies in eight of the newborn infants (table 2) indicate that the concentrations of circulating thyroxin, the hormone of the thyroid gland, are again considerably higher than those encountered in adult euthyroid subjects, and usually exceed even the elevations observed during pregnancy.[4]

B. Protein-bound Iodine Several Weeks Later: It is readily evident from table 1 that in older infants, 1 to 5.9 weeks of age, the levels decline again to the range

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* The authors are indebted to Dr. Florence Marcus for access to this second group of infants.

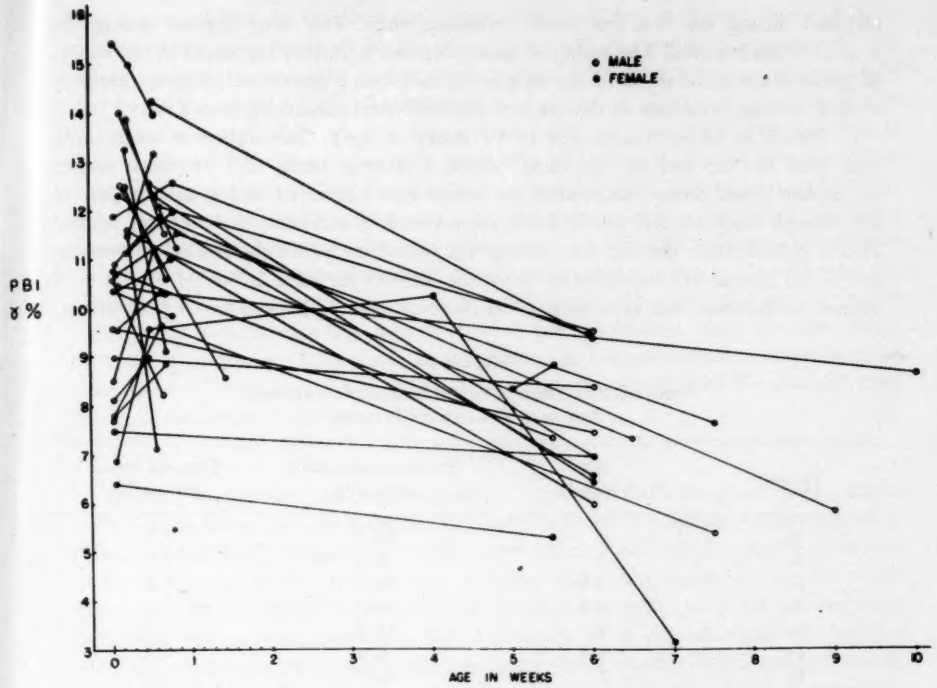

CHART 1. Serial protein-bound iodine concentration measurements in additional group of 38 infants ranging in age from 1 to 70 days. General trend downward is evident beyond 1st wk. of life.

TABLE 1

STATISTICAL ANALYSES OF PROTEIN-BOUND IODINE VALUES IN INFANTS UP TO 1 YEAR OF AGE

Age	No. of Infants	Mean ± S.D.	Comparison with PBI in pregnancy* "t" test	"p"	Comparison with euthyroid adults† "t" test	"p"
0–11.9 hr.	20	8.3±2.4	1.28‡	0.20	9.78	<0.0001
12.0–23.9 hr.	22	10.1±1.4	7.24	<0.0001	22.28	<0.0001
1– 3.4 days	14	12.0±2.4	9.64	<0.0001	21.03	<0.0001
3.5– 6.9 days	27	10.9±1.8	9.79	<0.0001	23.95	<0.0001
1– 5.0 wk.	10	7.4±1.8	0.88	0.37	6.86	<0.0001
6–11.9 wk.	40	6.9±1.8	3.16	0.0025	6.86	<0.0001
12 –52 wk.	21	6.3±1.0	4.88	<0.0001	4.71	<0.0001

* Mean ± S.D. of 81 analyses in 57 pregnant women including 13 mothers of infants in this series: 7.8±1.3.

† Mean ± S.D. of 89 analyses in 25 euthyroid adults: 5.4±0.7.

‡ In a separate comparison of protein-bound iodine of serum withdrawn simultaneously from 10 mothers and babies in this series again no difference could be demonstrated statistically between concentrations in the mother and in the infant within the 1st 12 hr. of delivery or birth.

recorded during the first few hours following birth. This drop persists during the 6 to 11.9 week period. The reality of these decreases is further supported by the results of serial observations in 38 of the infants. In each case a downward trend is ultimately evident, despite variations in the slope of the individual connecting lines (chart 1).

C. Values in Older Infants (12 to 52 weeks of age): The scatter of values indicates that by the end of the third month following birth, and at times earlier, the protein-bound iodine has reached the lowest values observed during the first year of life, though these are still above levels encountered in euthyroid, nonpregnant adults.[4] This is evident from the fact that during this period the protein-bound iodine averages 6.3 ± 1.0 gamma per cent whereas in mature subjects the value is 5.4 ± 0.7.[4] It is of interest furthermore that in a series of analyses of older children 3 to 13 years of age,

TABLE 2

SIMULTANEOUS PROTEIN-BOUND IODINE AND THYROXIN ANALYSES IN NEWBORN INFANTS

Patient	Age (days)	Protein-bound iodine (gamma %)	Thyroxin iodine* (gamma %)
N.	4	13.2	5.7
B.	5	8.9	8.7
C.	4.5	11.9	8.1
P.	0.5	10.7	7.8
L.	4	11.3	7.9
Cr.	0.5	6.4	4.8
G.	1	10.9	7.0
A.	1	8.0	5.4

* It is of interest to compare these values with those obtained in a series of 33 euthyroid control subjects in whom the serum thyroxin values averaged 3.7 ± 0.8 gamma per cent. (See reference 4.)

reported from another laboratory, the protein-bound iodine approximated closely the present authors' values for adults, rather than those for infants, averaging 5.5 gamma per cent.[9]

DISCUSSION

The aim of these studies has been the establishment of standards of reference for evaluating thyroid functions during the first year of life based on findings in healthy infants. The desirability of some objective index is of course frequently emphasized in clinical problems of retarded or accelerated growth and development. In view of the good correlation between the level of circulating protein-bound or serum precipitable iodine and thyroid function reported in cretins and in hypo- or hyperthyroid adults,[1, 10, 11] the data which have been presented should permit earlier identification of thyroid hypofunction during infancy.

An interesting finding, particularly since one might expect a postnatal depression, has been the observation that the protein-bound iodine of newborn infants increases even further during the first week following birth. This rise is more than cancelled by a subsequent decline. By the twelfth week most of the protein-bound iodine values in these infants fall within the range of 4 to 8 gamma per cent characteristic of euthyroid adults, but the mean remains significantly higher.

It is possible that the transient rise evident during the first week represents a decrease in serum water coincident with the loss of weight usually recorded during this period. This cannot explain, however, the higher values present during the first year of life. These may be related either to (a) the metabolic and endocrine changes of pregnancy, with transmission to the infant, or (b) the metabolic needs of the rapidly growing newborn infant mediated through an accelerated production and release of thyroid hormone. Other factors which might be involved include (c) accelerated release without increased production, (d) alterations in the characteristics of the plasma protein with which circulating thyroxin and protein-bound iodine are associated or (e) decreased utilization or excretion of thyroid products. The persistence of these findings into the end of the first year, and perhaps longer, argues against (a) and (c). Categories (d) and (e) at present remain only speculations. Though the second of these five possibilities seems the most likely, particularly in view of the increased levels of thyroxin, it is not possible to identify at this time which of these factors is operative. This should not detract from the utility of these studies as standards of reference.

Summary

Statistical comparisons indicate that within 12 hours of birth the serum protein-bound iodine of the infant is of the same order of magnitude, on the average, as that present in maternal blood during pregnancy or within a few hours of delivery. During the remainder of the first week of life there occurs a transient statistically significant increase in the mean value of this iodine fraction. During the sixth to twelfth week the concentrations fall below those present neonatally, but at this time or at any subsequent age up to 1 year, they are still on the average above those encountered in euthyroid nonpregnant adults or in older children. The possible relationship of these higher mean values in infancy to increased thyroid function in the rapidly growing infant have been mentioned with emphasis on the elevated concentration of circulating thyroxin.

Acknowledgment

The authors are indebted to Mr. Carroll S. Weil for assistance in the statistical evaluation of these data.

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SPANISH ABSTRACT

Concentraciones de "Protein-bound Iodine" en Recién Nacidos hasta un Año de Edad

Las concentraciones de "protein-bound iodine" del suero fueron determinadas por el método modificado de Barker, en 154 muestras de suero obtenidas en 110 niños cuyas edades variaron entre la del nacimiento y un ano. El valor medio obtenido en recién nacidos durante las 12 primeras horas después del nacimiento, fué de 8.3-2.4 gamma por ciento. Este valor fué similar al promedio obtenido en un grupo de 57 mujeres embarazadas, incluyendo 13 de las madres de los niños antes mencionados. Al final de la primera semana después del nacimiento, ocurrió un aumento pequeño, pero estadísticamente significativo, de las concentraciones de "protein-bound iodine" del suero. Este aumento desapareció subsiguientemente. Después de las 12 semanas de edad, los valores de "protein-bound iodine" bajaron al nivel de 4 a 8 gamma por ciento característico de los niños mayores y de los adultos, pero la concentración media fué significativamente más alta. Las determinaciones de tiroxina en 8 de los niños revelaron valores mucho más altos que los encontrados en el grupo de adultos normales y aun en exceso de los valores observados durante el embarazo.

Estos valores altos en niños normales están aparentemente relacionados con el desarrollo y crecimiento de este período, particularmente en vista de las altas concentraciones de tiroxina.

Estos estudios vienen a proporcionar, incidentalmente, "standards" para un rápido diagnóstico de la disfunción del tiroides en niños, de los cuales no se disponía hasta ahora para el grupo de esa edad.

125 DeSota Street

Pediatrics

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AMERICAN ACADEMY OF PEDIATRICS, INC. PROCEEDINGS AND REPORTS

THE PRESIDENT'S PAGE

NO ONE question has been asked more often of me and of the members of the Board than this: Now that we have reorganized and established the position of Executive Secretary and have created a position of Business Manager and a Program Chairman, will we now consider our organization one whose main function is the benefit of its membership? The Board considers the organization and its resultant benefit to the members primary and fundamental, but the ultimate purpose of our Academy is to further those "Objects and Powers" listed in the Constitution under Article III. I shall not quote this Article in full, but I wish you would read all of it.

ARTICLE III

"The object of the Academy shall be to foster and stimulate interest in pediatrics and *correlate all aspects of the work for the welfare of children* that properly come within the scope of pediatrics. The Academy shall endeavor to establish and *maintain the highest possible standards for pediatric education* in medical schools and hospitals, pediatric practice and research . . . to maintain the dignity and efficiency of pediatric practice *in its relationship to public welfare.*"*

The above quotation gives the real object of our organization as formulated by those who wrote our Constitution. The Executive Board believes this object to be the aim to which we are pledged. Details will be described in later columns, for we are organized to carry this out. The Academy will continue to correlate all pediatric aspects of the work for the welfare of children. As a society we will seek to maintain the highest possible standards for pediatric education. We will point out the relationship of pediatric practice to public welfare. By means of strong national committees dealing with child health and by reason of the survey and its subsequent interpretation and by working with other groups interested in child welfare, we have already gone a long way in blazing a trail to that goal our founders envisioned. We have no intention of losing what has been gained nor do we intend to lose our leadership in child welfare. Rather we propose to enhance it.

* The italics are mine.

Our membership is composed in large measure of practitioners. The Board, however, is deeply aware that it is also composed of those who are in the academic group and those whose activities are exclusively in public health. We also include in our membership those who have been or are now part time in each of these groups. It is our plan that every group in the Academy will be made an integral part of our organization. In implementing those parts of Article III which I have quoted this is absolutely necessary.

To this end the help of every member of our Academy is sought.

PAUL W. BEAVEN, M.D., *President*

Pediatrics

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SPECIAL SECTIONS

THE PEDIATRICIAN AND THE PUBLIC

AN OPEN FORUM

PAUL A. HARPER, M.D., *Editor*

Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy.

THE following communication is a lecture by Prof. Jørgen S. Dich of Denmark which was delivered under the auspices of the Scandinavian Area program at the University of Wisconsin. Professor Dich was visiting professor of Scandinavian Area Studies, 1949-50, and has since returned to his post in Denmark.

WHY HAS SOCIAL MEDICINE SUCCEEDED IN THE SCANDINAVIAN COUNTRIES?

By PROF. JØRGEN S. DICH*

The subject of this talk concerns social medicine in the Scandinavian countries, not socialized medicine. The term socialized medicine has a political bias which is not in conformity with the conception of social medicine in Scandinavia. Every step in the development of the Scandinavian social medicine program has been adopted unanimously by all parties, irrespective of their attitudes toward socialism itself. Political parties have advocated liberalism and opposed socialism with the same ardor with which they have supported the expansion of social medicine. In Scandinavia, therefore, it is not necessary to advise us to "Keep politics out of this picture." Politics have always been omitted, even to the extent that a phrase corresponding to the American "socialized medicine" has never been used in Scandinavia. And if you were to try introducing it, it would not be understood.

What is social medicine? It can be defined as an organization of the medical services according to a certain conception of individual or human rights and public obligations in

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a modern society. In all countries it is accepted that there are some basic needs which everyone has the right to satisfy, irrespective of income. Protection of personal freedom belongs to this group; so does education of the children. Now, in the Scandinavian countries a similar viewpoint is held with respect to the health of the citizens and the care of defectives. This conception is based upon two considerations. The first is a moral one. In a modern, wealthy Christian community it is an obligation of society to see that no person suffers more than is necessary from illness or from congenital or acquired disability. Help should be unlimited and carried on until a man is cured or until his death. This is a Christian obligation of democratic society towards its more unfortunate members—a fine materialization of the Scandinavian conception of Democracy and Christianity.

The second consideration is a practical one. Every civilized country protects its citizens against epidemic diseases and against more contagious illnesses without thinking of demanding payment in return for these services. This preventive part of the medical services is a form of social medicine. The problem comes down only to the question of: "Where shall we draw the line?" In the old days, the borderline was very narrow indeed. Social medicine in the Scandinavian countries embraced only a very small part of the total medical services. But in the course of time, it has proved very difficult to maintain rigid limitations, especially since preventive medicine has gained a more and more predominant position in medical science and policy.

It is repeated again and again by health authorities that early medical examinations are very important for successful treatment. The slightest ailment or other irregularity may be indicative of more serious illness, such as tuberculosis, cancer, etc. It would be in contradiction to this campaign if admittance to medical examination and treatment were barred by high charges. Only a free, or an almost free, medical service is in full conformity with the basic ideas of preventive medicine. From the very onset, Danish sick clubs, therefore, have provided free medical care. I shall return to this item later.

Broadly speaking, the foregoing concepts have formed the basis for the almost parallel development in the Scandinavian countries of a steady expansion of social medicine.

Can it really be of any value for Americans to study experiences with social medicine in other countries? Most Americans undoubtedly think that it can, since British experiences during the initial years of their social medical experiment have figured prominently in discussion about National Health Insurance bills.

The AMA put it this way, referring to Great Britain: "The greatest error in all history would be for America to start borrowing the unsuccessful system of foreign countries."[1] Harold Stassen summarized his report on the British system with the following declaration: "More medical care of a lower quality for more people at higher cost."[2] It is therefore quite understandable that his conclusion regarding the introduction of a similar system in the United States is "Never! Never! Never!" These declarations show that foreign experiences are used in the discussions. The question is, therefore, not whether foreign experiences should be used, but only how they should be used and which experiences are most valuable to apply and study.

I believe that those who want an objective evaluation of social medicine in foreign countries cannot confine themselves to a consideration of only Great Britain, with its two years of social medicine. If a businessman going abroad to study a new form of business organization limited his study to those of his colleagues who had just started such an organization, but paid no attention to those who had 50 years of experience, he would not

be considered a good businessman. The British Labour Government inherited a population which had suffered from inadequate medical care, by and large, for a generation. The plan it inaugurated has, furthermore, attempted to do too much too fast.[3] The British suffer from a shortage of doctors and dentists, and they have committed mistakes which might have been avoided if they had studied the Scandinavian experiences more thoroughly.

The Scandinavian countries with more than half a century's experiences have a certain "know-how" in this question—no doubt more than most other countries, not only because they have felt the impact of their medical system every day in their own lives, but also because this problem has been studied in numerous voluminous reports.

I should, however, like to stress that Scandinavians don't pretend to know anything of the advisability or possibility of introducing similar systems in other countries. No person can maintain that democracy, or the cooperative movement, or social medicine, or any other form of social organization having attained success in one country can, *ipso facto,* be introduced in another country with the same success. The application of foreign experiences and their adjustment to specific interior institutions, including the mentality and standard of living of the population, is a special art which can attain positive results only if performed by impartial and scientific thinking natives in collaboration with foreign experts. I will therefore abstain from any comment on social medicine in this country and confine myself to a discussion of the Scandinavian countries, focusing on problems which have been raised in the American discussions and propaganda.

The backbone of the medical system in the Scandinavian countries is the central and district hospital. Thanks to the fact that the responsibility of providing the country with hospitals was put upon the local authorities at a very early time, and that these local authorities took that responsibility seriously, hospital construction is a purely public affair and there has been no need for private business or private philanthropy. Apart from a few Catholic and Lutheran hospitals, there are thus no private hospitals in Scandinavia. This development automatically solved the problem that has been so difficult to cope with elsewhere, since there is only one kind of hospital in Scandinavia receiving the sick of all classes on the same very cheap terms regardless of their pecuniary standing, etc. All that is required to hospitalize a patient is an admission card issued by a practitioner.

The fees are extremely low. In Copenhagen the fee is 25¢ a day; in some provincial hospitals it is higher, but it never exceeds one dollar. Members of the sick benefit clubs don't pay anything at all. Hospital bills are paid by Health Insurance in Denmark for 6 months during a period of one year, and then 6 months again for the next period of one year, and for two years in Norway. Blue Cross in this country* pays for 31 days.

Persons who want private room, or who do not reside in the county or the town where the hospital is located, will be charged higher fees. The care in the hospitals includes every treatment necessary for a complete cure, i.e., drug, laboratory work, x-rays and operations, without any extra charge. If it is important for your treatment, you will get a private room with no extra charge. But I must add that the staff doctors have a right to take private patients, and in that case they are entitled to charge for their personal services, i.e., operations, but not for the ordinary hospital care (x-ray and so on). The charges are not high. They will only in rare cases exceed $50. Charges are in the main equal for all. The principle of charging what the "traffic can bear," which had some influence 50 years ago, has disappeared almost completely. It is no longer considered fair.

* The United States.

A commission in Denmark proposed in a report a year ago that all existing small fees on public hospitals and clinics be abolished, thus following Sweden where all charges for hospital stays and medical care at the hospitals will be eliminated this year. This was done for two reasons: First, to abolish bureaucracy and red tape involved in giving state support to the health insurance societies to enable them to pay the county or the state for the hospital services; and secondly, because the following opinion has become more and more widespread—"Why not consider a small country such as Sweden with only six million inhabitants as one health insurance company? The entire population is exposed to hospitalization in the course of a lifetime, and why not pay for that as a part of your taxes?"

Have these low rates entailed an abuse of the hospitals? This has been maintained with special reference to Germany (I quote from a pamphlet published by the National Physicians Committee, Chicago) that "patients sought admission to the hospitals for all sorts of minor illnesses and pretended sickness when they were not really sick."[4]

In the Scandinavian countries you cannot enter a hospital without first having had an admission card from a general practitioner. The diagnosis of your doctor is furthermore checked by the doctors at the hospital, so you can't be admitted until after two examinations. Abuse of the admission policy is, therefore, not possible. Hospitalization has, it is true, become more common in the course of time, but that is a result of progress in medical science and is not due to the cheap rates since they have existed for the major part of the population for 50 years.

The average period in the hospitals has been declining from 33 to 23 days. Among many other things this has been due to more intensive treatment as a result of improved equipment and the progress of science.[5] The stay is considerably longer than in the United States, where in nongovernmental general hospitals in 1948 the duration of hospitalization was only 8.2 days.[6] Danish doctors maintain that the length of the hospital stay is necessitated by medical causes, and that they always release the patient as soon as possible.

Patients often complain that they are sent home too early. Here is, however, a point where a detailed comparison between American and Scandinavian hospital conditions might be interesting. Part of the explanation may be found in the fact that all old sick people can enter the hospitals in Scandinavia without cost to themselves. Thirty-eight per cent of all deaths in Denmark, therefore, now occur at hospitals. Every sick or dying old man or woman is able to get the best medical treatment in the same hospital where you will find the millionaire. This, I believe, is democracy.

The Scandinavian hospitals differ, however, from the American ones in another and more important aspect. All Scandinavian hospitals have regular staff doctors whose entire working day normally is spent in ordinary hospital work and operations. General practitioners and specialists who are not in a hospital career are never allowed to treat their patients in the hospital. All treatment in the hospitals is, therefore, in the hands of specialists. Most operations require so much experience and skill that only doctors who have had many years of training with gradual progress from easy to more complicated cases under the constant supervision of the chief medical officer, and who, furthermore by daily exercise maintain their skill, are supposed to be able to take the responsibility of operating. Because of the high qualifications of the doctors at the hospitals nobody is interested in calling the family doctor or even a specialist to the hospital. Doctors as well as patients agree that the existing division of labor and the subsequent specialization benefits all of them. None has ever proposed any changes.

The doctors at the hospitals are paid fixed yearly salaries, but chief physicians and most of the older doctors have, as I mentioned before, the right to treat private patients also.

Another unusual feature in the Scandinavian hospital system is its financing. District hospitals are almost exclusively financed by local taxes. Hospitals in Denmark have not received any State subsidies at all (with the exception of small subsidies after World War II). County and town taxes pay not only the cost of construction and equipment, but also the total yearly deficit—which almost equals the total maintenance cost, including salaries to the staff, because of the extremely low income from hospital fees.

More interesting, however, is the fact that tax revenues in the countryside stem solely from property taxes, primarily paid by the farmers. Since farmers have the majority in most county councils and have nevertheless voted in favor of all appropriations, they pay, so to say, out of their own pockets to build and run hospitals open not only to themselves but to all persons living in the county.

But this is not all. Because of better means of transportation, progress in medical science, and the cost of much apparatus, a system has been adopted whereby one central hospital in each county is equipped with special departments, all modern apparatuses, etc.

It is not difficult to have the counties finance these general hospitals, but, as a county sheriff (the local representative of the Crown) declared some months ago, it is difficult to explain to the members of the councils why only one hospital in each county should have this complete equipment. They feel that all hospitals should be on the same level. They do not quite understand that because of the fine collaboration between the hospitals such a development is unnecessary and would only entail a waste of money and of qualified personnel. So you will realize that the problem is not, as in many other countries, that of inducing local governments to build hospitals, but of preventing them from doing too much. The explanation of this attitude is to be found partly in the historical development, partly in the mentality of the population— a strong feeling of compassion and responsibility for sick people. A sort of practical Christianity, you might call it.

It is a matter of course that the towns and counties which have financed the hospitals operate them themselves. They appoint a committee which is in charge of the hospital. The chief medical officers attend the meetings, but are not members and have no right to vote.

Let us now proceed to another aspect of social medicine—the question of medical attention by general practitioners. Here I must make some remarks concerning the health insurance system. In Sweden the insurance is still voluntary. But three years ago the Swedish Parliament decided to proceed to compulsory insurance by 1951. The reason for this change was twofold: First, the coverage of voluntary insurance was unsatisfactory—only half the population was included; and second, voluntary insurance involved a great deal of superfluous bureaucratic work in collecting contributions, checking influx and outflux of members, bookkeeping, auditing, etc. In a compulsory insurance all this work can be abolished by collecting contributions in connection with already existing taxes. That is what will happen in Sweden. The contribution will appear as a special item on the tax bill. If, however, you are not able to pay your tax, including your contribution to the health insurance, you will not lose your right to the medical services under the system, in the same manner as a nontaxpayer does not lose his right to police and fire protection or his right to the free education of his children.

In Denmark and Norway, on the other hand, advantages are based on membership

in insurance groups. Membership in Norway is compulsory for employees under certain income limits. It is estimated that 70% of the gainfully occupied part of the population belong to the insurance system. Voluntary membership, however, is allowed for all persons irrespective of income. Before the Norwegian Parliament, however, is a proposal submitted by the Minister of Social Affairs to extend the compulsory insurance plan to the entire population. The expenditure incurred by the plan will be met partly by a national insurance tax and partly by state and municipal contributions.

The insurance in Denmark is voluntary; 90% of the population is eligible, and 90% of these have been assigned membership, i.e., 80% of the population is insured. But a commission where the doctors had the majority proposed unanimously the shift over to a compulsory system with the contribution collected along with the income taxes. All Scandinavian countries are therefore, on their way to an all-comprehensive compulsory system since it allows cheaper administration and leaves no person unprotected.

AMA puts much emphasis on the differences between voluntary and compulsory insurance. We hear that "Voluntary Insurance is the American Way," "Compulsion is the Key to Collectivism," and in some cases also to Fascism or Communism. In the Scandinavian countries everybody looks upon these things without excitement. We take into consideration what is cheapest, what will contribute most to increasing the standard of health, and what is most just and reasonable.

Now, it is easy to realize that the appraisal of a system in relation to the doctors can only to a minor degree depend on its character of being a compulsory or a voluntary one, and that the crucial point in explanation of the doctors' attitudes is to be found elsewhere; particularly in the composition of the management of the insurance, the principles guiding the fixing of doctors' fees, their size, etc.

The management of the voluntary Danish sick benefit clubs (there are not less than 1,600) is, and has always been, in the hands of laymen. The clubs constitute a cooperative association of patients. The members pay their contributions—which cover 75% of the expenditures—and they elect their board of directors at general meetings. I have never heard that they have chosen a doctor at these meetings. The Royal Sickness Insurance Board (appointed by the King) counts no doctors among its members. This layman administration is considered a matter of course and has never been under discussion. It is based upon the general administrative theory that policy-making and control should not be in the hands of those specialists or technicians who should themselves be controlled. Policy-making primarily requires an evaluation of technical knowledge and skill in relation to other public needs and interests. For this purpose technical—in this instance, medical—knowledge is unnecessary, and may conceivably be detrimental by introducing an undesirable bias in regard to the protection of professional interests.[7]

To avoid misunderstanding, I must add that the Royal Medical Board—the advisory organ to the government in all medical questions outside the Health Insurance—is made up of physicians.

The next question is: who determines the fees of the doctors in the Danish voluntary system? Fees are fixed in a collective agreement between the Association of Sick Benefit Clubs and the Danish Medical Association, which is the strongest trade union in the country. The fees, therefore, are not decreed by the government, and the doctors cannot be considered civil servants. They work on a contract basis in the same way as doctors in this country work for some insurance companies. Even if a compulsory system should

be introduced, the wage-fixing procedure will not be abolished. The same principle is used in setting the dentists' fees. And, incidentally, after April 1 this year the sick benefit clubs in Copenhagen will discontinue free dental service to their members because they could not agree with the Dentists' Association on the fees. The contract, therefore, has expired.

As to the rate of fees, the most characteristic feature is that there is a reasonable relation between the doctor's fee or income and that of the major part of the population. One contributory cause has been that no large and wealthy middle class has tempted the doctors to raise their fees with the effect of pricing themselves out of the market for the large part of the population of small means. The existence of the sick benefit clubs, which already before World War I was an important source of income for the doctors and now is all-decisive, has had a controlling influence on the development.

The income of the general practitioner is, nevertheless, good. Lawyers and doctors have the highest income among persons with an academic education. Because of the difference in price level it is difficult to express in American currency the income of a doctor. But I would guess that the standard of living of a general practitioner with the highest number of patients allowed will range about $8,000—at a rough estimate. This is a fair income, because few have higher. Specialists and chief officers in the hospitals earn more, twice or in some cases three times as much. On an average, doctors rank sixth among the groups with the highest incomes—managers, stockbrokers, lawyers, wholesale dealers, and owners of factories ranging higher. The average income of doctors is three times the average income of workers.

Dr. J. G. Crownhart, onetime Secretary of the State Medical Society in Wisconsin, reviewing the experiences of Denmark, said in 1938: "Sickness insurance is a leveling device which assures the mediocre physician just about the same reward as the man who renders outstanding service. . . ."[8]

There is only one thing to say to that: It is not true. The income of the doctors depends (with the exception of that part of the hospital doctors' pay which is salary) exclusively on the number of patients who choose him as their family doctor or on the amount of his services.

Both fees paid on a per capita basis (according to the number of patients on the doctor's panel) and fees paid for services are used in Denmark, in the towns and outside the towns, respectively. These two systems are both approved by the Medical Associations. These principles permit a sound competition among the doctors, resulting in better services and a wide spread in the income of the doctors.

To avoid "assembly line service" an upper limit on the number of families on a doctor's list has been fixed. It is 2,500. For the sake of comparison, I must mention that the limit in Great Britain is 4,000,* which according to Scandinavian experiences, is much too high. In addition, a doctor may, of course, have as many private patients as he wants.

I should like to add that the doctors may settle down where they want in the countryside and begin competition with other doctors. Where the panel system prevails, they have to get an approval from one of the sick benefit clubs. There are 36 of these in Copenhagen alone.

Now let us look at the picture from the patient's point of view, which, of course, should be the most important. Doctors are, after all, only servants of the public. First

* People (editorial comment.)

and foremost, patients in all three countries have the right to select a doctor of their own choosing. This is almost considered as a human right. Where the panel system exists, it is necessary for practical reasons to confine the right to a new choice once a year. Admittance to a specialist is furthermore dependent on reference from a general practitioner unless a patient wants to pay the specialist himself. In Denmark the sick benefit clubs are obliged to provide their members with free medical service by general practioners, and almost all of them give, in addition, free service by specialists and dentists (only extractions and ordinary filling; not gold-work or dentures). That is to say, the insurance covers all doctors' bills, not only for office calls, but also for home calls. The only exceptions are Sunday calls and night calls. In the countryside there is a small control fee of 25¢ for each call which is paid to the club, not the doctor.

In Sweden, however, you have to pay one-fourth of the doctor bill yourself, and the doctors are entitled to charge more than the basic fee agreed upon with the sick benefit clubs. A commission headed by the general medical officer, however, has taken this up for revision and proposed a switch to a system very similar to the Danish one. The same is true in Norway.

A very crucial point is whether this system is abused. David M. Heyman feels that "malingerers and hypochondriacs have needlessly been taking up the doctors' time" in Great Britain.[9] I have officially discussed this problem with outstanding representatives of the Danish Medical Associations and they do not talk about abuses. Hypochondria is a disease, and some real cases may, of course, occur. But after all, it takes time and, for some persons, a loss of income to consult a doctor. Most patients have respect for the doctors' job, so needless calls are few. The disadvantages of some unnecessary calls are, in the opinion of the doctors, counteracted by the great advantages of the free system. The doctors have never proposed any changes in the system. In the countryside where the doctors receive a fee for each call, one might perhaps have a suspicion that their attitudes are based on the fact that they have an economic interest in a large number of calls. But in the towns, where the doctors receive a yearly fee for each member on their list, their stand is the same. The explanation is, therefore, more to be found in a feeling of responsibility to their patients, and in an understanding of the enormous importance of free medical services from a preventive point of view. Doctors know from experience that the earlier they start treating a patient, the better will be the results and the fewer calls they will have in the future. They, therefore, devote a great part of their energies to the prevention of illness.

The free medical service is only one aspect of the preventive program. I should like to mention that almost all preventive medical care for expectant mothers, infants, preschool children and school children is free of charge in all three Scandinavian countries. Health nurses examine all infants in most of Denmark up to 24 times during the first year. Swedish women have free travel privileges to visit doctors or child welfare centers during pregnancy, and after childbirth for several free examinations. School doctors for preventive examinations are, or will be in a few years, in all public schools.

Free dental treatment for school children is expanding, and as soon as the shortage of dentists has been overcome, will cover all schools in the three countries. In this connection I want to mention that Norway and Sweden deliberately have postponed the implementation of their comprehensive plan of a nation-wide social dental service for one important reason: shortage of dentists. For the same reason Denmark cannot for the

first years expand social dentistry further. The countries realize that it would be most detrimental to any improvement of a system if from the start it should suffer from overburdened and dissatisfied doctors or dentists, and consequently, dissatisfied patients too. The right pace in development is an essential item. Going too fast as well as too slow leads to socially undesirable results.

In the discussion of social medicine so much attention is focused on the position of the doctors and the ordinary patient that one often skips a very important part of social medicine: the so-called special care for such unfortunate persons as the feebleminded, insane, blind, deaf and dumb, epileptic and crippled patients in hospitals, institutions, special schools, orthopedic hospitals, and so on. All treatment of these defective persons is free of charge in the Scandinavian countries, with the exception of a small charge to be paid for persons of high income. No family fears to have its children or relatives at a mental hospital or an institution for feebleminded because it knows the quality of the medical treatment and it knows that everything will be done to make the lives of the institutionalized as bright as possible under the conditions that nature has imposed upon them.

Part of this special care is in the hands of the State, part in the hands of private nonprofit organizations, but up to 99% of the expenditure is nevertheless paid out of public funds.

I cannot find any other explanation for the outstanding level of all these institutions unless it arises from some special feature in the mentality of the population. Individualism has never reached such a point that Christianity has disappeared in human relations. This feeling of obligation towards the physical and mental defective has, in the course of time, induced the parliamentarians to appropriate the enormous amount necessary for the expansion of the special care for invalids and handicapped.

On the other hand, in the explanation of the development of the Health Insurance system I do not believe that too much emphasis must be laid on such moral qualifications. Much of the development can be explained with reference to other human qualities. Let me mention some:

1. Cooperative initiative has in these spheres come earlier than private. The farmers, and after them the workers, started their own cooperative sick benefit clubs in the '80s, even before private insurance companies entered this field.

2. State and local governments were interested in supporting sick benefit clubs in order to have the people insure themselves, and thus lighten the burden on the public in case of sickness.

3. The doctors were interested because when dealing with a sick benefit club they were certain of their fees, whereas a great many people of small means had difficulty in paying their bills in the beginning of this century, and often did not pay before they were sued. The doctors have, therefore, never opposed the development. At the initiation of this plan they may have supported it because it meant some economic advantages—doctors are as interested in money as all others—but in the course of time their mentality has changed considerably, and they now support the system as the best from a medical point of view.

4. In Sweden and Norway, especially, large steps have been taken after Labor obtained the majority in Parliament. In a democratic society the majority in the long run always gets what it wants.

That leads us to the next point. Has the population been mistaken? Has it backed an unsatisfactory system, or has this system been successful? The answer to these questions depends upon the objectives which a medical system aims to fulfill. I would say that the first objective is to secure a high quality of medical services as a whole, and the next is to give these services to everybody irrespective of economic resources.

The quality of medical services depends on a large variety of factors:

1. The education and training of doctors at the universities. I only mention that the doctors have a seven or eight year course of strenuous study and thereafter one year of obligatory hospital service. As this education, however, is independent of the character of the medical system, it is of minor interest in this connection.

2. Another factor is the right specialization among doctors: staff doctors at the hospitals with the highest possible training are exclusively occupied with their specialties. Highly trained specialists, approved by the Medical Association outside the hospitals, are not overburdened with trivialities because only complicated cases are referred to them. There is no fear among the nonspecialized general practitioners to refer patients to specialists because they know that the patient will be referred back to them after having been diagnosed and/or treated by methods requiring advanced medical education. All this raises the quality of medicine.

3. A third factor is the good collaboration between doctors and hospitals, not only for treatment, but for diagnoses too. All hospitals have diagnostic departments where the general practitioner may send his patients for diagnosis.

4. Hospitals of high quality are of the utmost importance for the quality of medical care. Because of the willingness in county councils and towns to appropriate funds for building, extending, and improving hospitals, the hospitals, especially in Sweden and Denmark, are outstanding. The Swedes have just published a beautiful book on Swedish hospitals in which they write that the objective of the volume is to inform foreign audiences about the splendid development of this most important part of Swedish social life. This is conceited talk, but it is not unjustified.[10]

5. A fifth factor determining the quality of a medical system depends upon a sufficient number of doctors and hospitals, and an even distribution of these over the country. There are more doctors per 10,000 inhabitants in the United States than in the Scandinavian countries. The United States has one doctor per 700, Denmark one per 952,[11] while Sweden and Norway have somewhat fewer. I don't believe that the smaller number is due to the social medical system, but rather to the smaller number of families who have been able to pay for the medical education of their children—in spite of the fact that there is no tuition at Scandinavian universities and medical schools. When the number of doctors is fewer, their utilization is better because they are evenly distributed over the country, not only in Denmark—which has a density of population seven times greater than that of the United States—but in the main in Norway and Sweden too. It is true that the increase of population and progress in science lead to a demand for more doctors, but no lack of doctors is felt in Denmark, and the doctors are not overburdened with work.

There are more hospital beds per 1,000 inhabitants in Denmark than in the United States—11.3 in Denmark, 9.1 in the United States.[11] These figures comprise beds in all hospitals. The number of beds in general hospitals, exclusive of beds in hospitals operated by the Federal Government, is 3.2 per 1,000 inhabitants in the United States,[12]

4.8 in Denmark. Danish hospitals are evenly distributed over the country; no home is farther than 12 miles from a hospital.

6. Another important factor to promote the quality of medicine is the inducement to doctors to do their utmost. As a certain competition is necessary to create this inducement, it is maintained. The payment of fees on a per capita basis will, in addition to the competition, also increase the doctor's interest in good preventive medical care.

7. Finally, we should not forget the widespread ramifications of the free preventive medical care and the free care for all mentally and physically defective persons.

The medical system of the Scandinavian countries is, therefore, on a very high standard. A gentleman declared in this room half a year ago that 90% of his objection to social medicine was that it would entail a deterioration in the quality of the medical services. I do not know if that is a correct prediction for this country. But in the Scandinavian countries this has not been true. On the contrary. A major reason for introducing social medicine in Scandinavia was the desire to increase the quality of services in hospitals, in institutions for defectives, and outside the hospitals—to increase the standard of health of the entire population.

Comparisons are difficult. But a friend of mine, a well-known professor of medicine in one of our universities who studied medical services over here after the war, was enthusiastic about the quality of some very outstanding hospitals in the United States. He felt, however, that the services performed by the average hospital and the general practitioner were inferior to that of Denmark. On the other hand, AMA's President, Elmer L. Henderson, declares: "U.S. medicine is the finest in the world. . . ."[11] I don't know who is right. Maybe Mr. Altmeyer, Chairman of the Social Security Board, can serve as mediator with the following comment: "U.S. has *among* the finest hospitals, the best-trained and the most skilled physicians in the world."[13]

But this statement does not solve the question of the quality of services inside and outside hospitals in Scandinavia in comparison with the United States or other countries. A thorough investigation on this point, therefore, would be useful.

The next great objective of social medicine is, as I mentioned before, to remove any economic barrier between the individual and his access to whatever health or medical services he requires. My previous remarks prove that this side of the social medical system has been achieved fully in Scandinavia. The poor and the rich receive the same treatment—the best!

Is it not a proof of success that all legislation has been adopted unanimously; that the system enjoys the support of the entire population, including the doctors without exception; that the only proposals submitted have been to expand the system even further, to make the system even more a real social system?

When you now ask me why this system has succeeded, I can answer by referring to the various reasons for its development already mentioned and to the well scrutinized provisions carried out in the course of time to maintain equilibrium and avoid possible abuses.

All these things do not have too much to do with the size or the homogeneity of the countries, but more with a certain mentality—a social consciousness and a feeling of social responsibility. This mentality has not existed forever. It has grown up gradually, partly as a result of the impact of social legislation. The development has created a mentality which has supported further development.

Finally, some remarks on the economic side of the question. It is often maintained that any social or compulsory system entails an unbearable burden on society. Is this true for the Scandinavian countries? I should like to mention that the health of a population is so important that the best is not too good—and the best is not cheap. The total administrative cost in Denmark, which still has a voluntary system, is in most clubs $1.50 to $2.00 per year per member. Even if you take into consideration the difference in purchasing power, this is low. The reason is that there is no advertising, no agents running around, no profit, and much work in the small clubs is done gratis or for small fees. But even these expenditures are considered too high. That is one of the reasons why a compulsory system has been proposed. The development of the medical schemes in the Scandinavian countries from voluntary to all-inclusive systems is, among other things, brought about by a desire to diminish administrative waste, red tape and bureaucracy.

The whole system is not too expensive because of the previously mentioned reasonable relation between the doctors' incomes and that of the broad masses of the population. The total expenditure for medical care in the United States amounted in 1948 to 4.1% of the national income.[14] The expenditure in Denmark for sickness insurance and public health, including care for tuberculars, epileptics, insane, feebleminded, and alcoholics, will not exceed 3% of the national income.[15]

I believe that I have proved that the system has been a success not only from a medical and humanitarian, but also from an economic point of view. A summary of social medicine in Scandinavia would be: More medical care of higher quality for all people at lower cost!

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TRENDS

By JOHN P. HUBBARD, M.D., *Contributing Editor*

This and subsequent descriptions of events and trends are intended to be unbiased and factual, presenting both sides of controversial matters so that conclusions may be formed from critical appraisal of things as they are. These statements do not necessarily reflect the opinion of the writer nor are they to be interpreted as official opinion of the Academy.

THE LOCAL PUBLIC HEALTH UNITS BILL

A MONTH ago in this column, we drew attention to the status of the Local Public Health Units Bill as it stood in early December in the 81st Congress. We have been watching with special interest the further course of this Bill in view of its direct relationship to the oft' expressed objective of the Academy to extend child health services into areas of need. One of the needs most clearly demonstrated by the Academy's study results from the inequity of health services in rural and isolated areas in comparison with metropolitan areas. The Local Public Health Units Bill proposes to stimulate the development of local health departments, one of the recognized functions of which would be an extension of maternal and child health services. The support which this Bill has received and the fate of this Bill in the 81st Congress may be summarized by the following quotations:

In his presidential address, presented at the Fourth Annual Clinical Session of the AMA in Cleveland, December 5 to 8,* Dr. E. L. Henderson said: "The American Medical Association has long believed that the existence of effective and properly operated public health units is basic to the maintenance and improvement of the health of the people. As early as 1883, a report was made at the annual meeting of the Association covering a survey conducted to ascertain what states and counties had health departments. In the years that have followed, our interest in the subject has remained unabated. Resolutions have been adopted by the House of Delegates urging complete coverage of the nation's population by county, district or regional full time modern health units. Point 6 of our 12 point program gives proper and additional emphasis to the important role that public health departments must continue to fill in our ever-expanding and untiring efforts to provide the people with better and better health care. Tremendous progress has already been made; much more needs to be done.

"I stress this subject because, unfortunately, action taken by the House of Delegates at the San Francisco meeting in June 1950, with reference to a bill in Congress to authorize federal financial aid for the development of health departments, has led to misunderstanding of the present point of view of American Medicine toward the development of such programs.

"Did the San Francisco action, in effect, reverse the previous and long-established position of the Association? This is a question that is being asked. In order to remove any doubt about the matter, I should like to suggest that the House give consideration at this session to reviewing the action taken earlier this year for the purpose of clarification. In my judgment, such a review now would be most timely."

In his weekly column in the Sunday *New York Times*† Dr. Howard A. Rusk said, in

* J.A.M.A. **144**:1268 (Dec. 9) 1950.

† *The New York Times*, Sunday, Dec. 10, 1950.

reference to civil defense plans: "As W. Stuart Symington reported to the President in September, all planning done on the health and medical aspects of civil defense is based on using state commissioners of health as directors of civil defense health services, and local health officers as directors of local civil defense health services. This plan has been accepted as a most practical and effective administrative mechanism, but unfortunately, nearly 30 per cent of our citizens live in communities in which there are no full-time local health services.

"Only six states in the nation now have complete local health services coverage in all counties. They are Maryland, Delaware, New Mexico, South Carolina, Alabama and North Carolina, which added its final county recently.

"There is almost complete coverage in California, Michigan, Florida and Virginia. Kentucky, Louisiana and Tennessee have organizations for nearly every county, but have many health officer vacancies.

"Steps toward remedying this situation were taken last year when the Senate, with bipartisan sponsorship and wide public support, unanimously adopted a bill authorizing Federal grants-in-aid specifically for local public health departments. The act provides Federal funds for at least six minimum functions of a local health department: vital statistics, communicable disease control, maternity and child hygiene services, environmental sanitation, public health laboratory services and public health education.

"As Dr. William P. Shepard, president of the American Public Health Association, said recently, 'Public Health services are the administrative backbone of civil defense. The immediate development of such services is not only requisite to the safeguarding of the health of the nation in normal peacetime, but is given even greater urgency by the current demands for the establishment of adequate civilian defense against possible acts of aggression, including atomic, biological, chemical and other devices of warfare directly affecting the civilian population.'

"That there is urgent necessity for immediate action by the House of Representatives is clear. One-third of the nation is without the administrative organization for providing even normal local health services, let alone those necessary for civil defense. The provision of those services is as essential to our civil defense as weapons are to our fighting men."

In the *Washington Report on the Medical Sciences* for December 11, 1950, Gerald Gross comments as follows: "House Rules Committee on Friday 'postponed action' on the question of increased Federal support of local public health units, thereby adding to the list of shelved bills branded as undesirable by American Medical Association. Twenty-four hours earlier, in Cleveland, AMA's trustees had turned thumbs down on bill in question (HR 5865) and its action was the decisive factor in committee's rejection of an appeal by J. Percy Priest, House leader on health legislation, for granting of a rule that would permit a floor vote on HR 5865 by the full membership."

In order to clarify the position of the American Medical Association in relation to the Local Public Health Units Bill, we wrote to Dr. George Lull and have received from him a letter under date of December 29, 1950, from which the following is quoted:

"The American Medical Association prior to June 1950 supported HR 5865 and S 522, which are identical, but made specific recommendations for amendments which were only partially adopted by the Congressional Committees concerned. Because these recommendations were not wholly adopted, the House of Delegates of the American Medical Association in June 1950 at the San Francisco Session of the Association voted

to oppose HR 5865, although continuing to endorse the general principles contained therein.

"The objections to HR 5865 fell into two principal categories: (1) The bill placed local health units under the direct and complete control of the Surgeon General of the Public Health Service. No advisory council was provided to check the power vested in the Surgeon General. (2) Public Health services were defined, in part, as 'the detection and diagnosis of chronic diseases and such other services concerned with the maintenance, protection or improvement of the public health as the Surgeon General may prescribe.' The American Medical Association consistently opposed this vague terminology which would have permitted any kind of federally subsidized health activity by local health departments. For example, the diagnosis and treatment of cancer, heart disease, arthritis and other chronic disease, previously considered outside the proper scope of public health departments, could have become a health unit activity. The Association opposes the use of federal grants-in-aid to the states for initiating local programs that have never been considered within the province of public health. There are many noncontroversial projects such as communicable disease control, sanitation, public health education and others for which there is need for local expansion, without moving into new areas.

"On December 8 the House Rules Committee voted not to report HR 5865 to the floor of the House, partly because of the objections of the American Medical Association to the provisions cited above and partly to other objections raised by committee members. It has been reported that these latter objections were based on the urgent necessity to conserve federal funds for those activities related to national defense and the belief that federal financial support of local health units should be restricted to defense areas.

"Mr. Priest, the Chairman of the House Committee on Interstate and Foreign Commerce, introduced on December 10, 1950, HR 9914 which answers some of these objections. This bill was an improvement over the previous one, but it still contained certain objectionable provisions and omitted protective measures that the Association considers essential. For example, under the term 'basic public health services' were included 'laboratory services.' We believe this should be amended to read 'public health laboratory services.' Also, under this section provision was made for excluding medical and dental treatment except as necessary for communicable disease control and epidemic or other emergency situations. We feel that medical *diagnosis* as well as treatment should be excluded. Finally, and most important, the bill still did not include an advisory council which could serve as a check on the broad grant of power given to the Surgeon General.

"It should be appreciated that all current legislation needs to be reexamined in the light of the present grave international situation to assure that our total effort is directed to the strengthening of the national defense. The Priest bill, HR 9914, provided that federal funds for local health units be allocated primarily to areas in which civil defense needs are paramount. This provision was a step in the right direction.

"A bill similar to HR 9914 will be introduced at the beginning of the 82nd Congress and conferences between Congressman Priest, the Public Health Service, the American Medical Association, and other interested groups will continue for the purpose of developing a bill that will be satisfactory to everyone concerned.

"The American Medical Association does support adequate local health services for the nation. The present negotiations are designed to develop a bill that will support these services without resulting in complete federal control of local community programs."

PUBLIC HEALTH, NURSING AND MEDICAL SOCIAL WORK

MYRON E. WEGMAN, M.D., *Contributing Editor*

PREMATURE BIRTH AS A WORLD HEALTH PROBLEM

By ETHEL C. DUNHAM, M.D.*

IT IS well known that prematurity plays an important role in causing infant deaths. Moreover, it is generally recognized that, to lower the high mortality rate from prematurity, concerted efforts are needed to lower the incidence of premature birth as well as to render proper care to these infants after birth.

The Second World Health Assembly directed the convening of an expert group on care of the premature infant, which met in Geneva from April 17-21, 1950. This report reviews the results of their deliberations,† illustrates their suggestions and recommendations from material made available to them by the WHO staff and adds some personal comments.

DEFINITIONS

First, the expert group on prematurity recognized the necessity for uniform terminology for international usage. The primary goal—to lower foetal and neonatal mortality—can best be achieved by providing specialized care for infants of low birth weight. They suggested that a premature infant be defined as one whose birth weight is 2,500 gm. or less but recognized the limitations of this criterion since birth weight will not always be available. Other criteria of prematurity must then be used, for example, gestation period. They therefore recommended the adoption by all countries, for purposes of vital statistics, of the international definition of the World Health Assembly 1948,[1] which states:

"For the purpose of this classification an *immature infant* is a liveborn infant with a birth weight of 5½ lbs. (2,500 grams) or less, or specified as immature. In some countries, however, this criterion will not be applicable. If weight is not specified, a liveborn infant with a period of gestation of less than 37 weeks or specified as 'premature' may be considered as the equivalent of an immature infant for purposes of this classification."

The expert group considered the question of setting a weight limit below which a premature birth should be considered an abortion. The majority of the group agreed that no such limit should be set for two seasons: (1) The exact lower weight limit cannot be set on the basis of present knowledge, and (2) such a delimitation would not be in conformity with the recommendations of the Sub-Committee on the Definition of Still-

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Adapted from a postgraduate lecture at the Sixth International Congress of Pediatrics, July 1950, Zurich, Switzerland. The original text of the presentation was published in the *Journal Suisse de Medicine* in the German language in 1950, No. 29.

† *Report of Expert Group on Prematurity,* World Health Organization Technical Report Series No. 27, 1950.

birth and Abortion of the WHO Expert Committee on Health Statistics. They concluded that "foetal death" should be defined rather than the term "still-birth" and that the definition of foetal death should be the reverse of the definition of live birth:

"Definition of live birth and live born:[2] Live birth is the complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of pregnancy, which, after such separation, breathes or shows any other evidence of life, such as beating of the heart, pulsation of the umbilical cord or definite movement of voluntary muscles, whether or not the umbilical cord has been cut or the placenta is attached; each product of such a birth is considered live born."

In regard to low birth weight as a criterion of prematurity, the WHO staff collected data on average or mean birth weights of infants in various areas in the world. These data showed wide variations. It is obvious that if the average birth weight of infants in an area is 2,600 or 2,800 gm., then a larger proportion of infants will be premature, i.e., weigh 2,500 gm. or less, than in areas in which the average birth weight is 3,300 or 3,500 gm.

Studies have shown that the infant's birth weight is influenced by various factors, among them race, sex and certain social and economic factors. For example, the mean birth weight was found to be 6% lower among infants whose mothers did not receive prenatal care than among those whose mothers attended a prenatal clinic (Johannesburg, South Africa). The average birth weight of illegitimate infants in Stockholm was about 10% less than the average for legitimate infants. Gross deficiencies in the maternal diet during conditions resulting from the last war affected the average birth weight of infants. For example, in Siena, Italy, the weights were 5% lower, in Greece 10% lower, in Vienna and in the Hague and Rotterdam, 11% lower than in times when the food supply was more adequate.

Gestational age is well known to be often inaccurate as a criterion of prematurity. For example, Hosemann[3] found that of 12,000 births in Gottingen the weights of those with a gestational age of 27 to 28 weeks ranged between 600 and 1,799 gm.; those with a gestational age of 37 to 38 weeks, between 1,400 and 4,999 gm. Conversely among 3,045 infants who weighed 2,400-2,599 gm. gestational age varied from 29 to 50 weeks.

Other criteria of prematurity, such as clinical evidences, development of ossification centres and characteristics of hematopoetic system, are unreliable or impractical to use. On the whole, then, the International Definition is the one for universal adoption at the present time.

Programmes

A. Reducation of Incidence of Prematurity

Reduction of the incidence of premature birth is obviously a problem of improving maternity care but concerns the pediatrician also since success in caring for the infant after birth is greater with greater maturity.

The development of a preventive programme is part of a general public health programme which should include strengthening and extending of prenatal services, public and private; making these services readily available to all pregnant women; providing for skilled delivery under conditions propitious for the infant as well as the mother; making adequate provisions for hospitalization of women with complications of pregnancy; educating women as to the benefits of such services; and studies to determine, in a given locality, the most frequent causes of premature labour.

It is obvious that the causes of premature birth vary in different areas within a given country and in different countries of the world. It is commonly said that in a large proportion of cases no cause is determined. It is probable that, in reality, it should be said that no cause was reported or no effort was made to determine the cause. A study in the USA seems to confirm this comment on my part. In the reports of 13 authors[4] the cause of premature labour was determined in 69% of the cases in one report and in only 35% in another. The more frequent causes of premature birth reported by these authors are multiple birth, toxemia, premature rupture of the membranes, syphilis, and antepartum hemorrhage. In India, on the other hand, malnutrition and anemia, in Manila, beri-beri in the mothers, are said to be the most important factors in causing premature birth.

The need to protect pregnant women from heavy work during the latter months of pregnancy as one means of lowering the incidence of premature birth is shown in a report from Roumania.[5] Among women who were "workers by the day" 22% of the infants were prematurely born; among agricultural workers, 20%; among cooks, 13%. Appropriate legislation to include periods of leave, indemnities during unemployment and guarantees of employment status are among the recommendations of the International Labour Office.

B. Premature Infant Care

In regard to specialized programmes for premature infant care the expert group recommended the following prerequisites:

1. Birth registration as complete as possible and data on the birth weight and/or gestation period entered on the birth certificate if possible;
2. Compilation of accurate infant mortality statistics and neonatal and foetal mortality rates;
3. Significant downward trend in infant mortality, particularly in the period one month to one year;
4. Qualified medical and nursing personnel;
5. Adequate hospital facilities and equipment which are available or can be made available;
6. Provision for adequate services to improve unfavourable social conditions of pregnant women.

As to the content of such a programme, the expert group made the following general statements:

1. In areas in which there are no organized programmes for premature infant care, the mortality rate of these infants is high compared with those areas in which such programmes have been developed.
2. The initial steps in the development of a premature infant care programme should be related to the pattern of maternity care in the country or area undertaking the programme, depending on whether the largest proportion of births is in hospitals or homes.
3. These programmes might well be started as demonstrations. In such demonstration plans, efforts should be made to ensure that all existing resources of the community be integrated into the programme, including such resources as public health and welfare agencies, official and voluntary, and professional personnel, including physicians, nurses, and midwives.

Hospital Care

The expert group then suggested certain minimum requirements for establishing a premature infant hospital unit. They recognized the fact that first and most important is the provision of qualified personnel to care for the infants. They said that there should be at least one qualified physician, preferably a pediatrician, with experience in the care of newborn infants, both premature and full term, to be in charge of the unit; at least one qualified nurse with special training in the care of premature infants to supervise the nursing personnel in the unit; and sufficient additional personnel to ensure adequate care for the infants at all times (day and night).

It should be re-emphasized that these are minimum staff requirements. Standards[6] have been set in areas where premature infant care is highly developed that can be attained by very few of the many areas in the world that need and desire to develop programmes. In my opinion, any group contemplating the development of a special hospital unit should set up the highest standards for personnel that are possible of attainment within their area. The greater the experience and training of the supervisory staff the safer the use of relatively less qualified assistants such as pupil nurses and nurses' aids. Moreover, the ratio of nurses to patients should be higher for premature infants than for any other group of patients.

Secondly the expert group stated that in selecting the site for the premature infant unit consideration should be given to providing protection from infection and easy access to mothers to encourage closer mother-baby relationships.

The implications of this brief statement are very comprehensive. The site must be considered first in relation to the general needs of the community and second in relation to the specific hospital. In France, for example, hospitals have been selected to serve as centres (1) on a geographic basis—for an area of 30 to 100 kilometers; (2) because they are university or medical school hospitals; (3) because, when not in Group 2, they have adequate qualified staff and have indicated a desire to serve an area of great need; (4) because of density of population and low economic status of the people.

Location of the unit within the hospital will vary according to the type of hospital and the plan for care. Provision must be made for hospital births, home births brought to hospital and for sick premature infants. In general, it is best to care for these three groups in three separate units and to provide separate personnel for each group if cross infections are to be prevented. To accomplish this is a serious problem, chiefly because the numbers of qualified nursing personnel are inadequate in every country in the world. Thought should be given to keeping the hospital case load as light as possible by limiting admissions to infants in the lower birth weight groups, those under 2,000 or perhaps 1,800 gm.; to discharging infants from the unit to their homes when they have attained a weight of 2,000 gm., or sooner if they are vigorous, and if home conditions are satisfactory for their care. Greater efforts should be made to have the mother participate, under supervision of a nurse, in the care of her infant. This educational plan for the mother will promote normal relationships and enable her to take the infant home as soon as it is felt that it is not a risk for the infant (see section on home care).

Facilities and equipment should include a separate bed for each infant; adequate facilities for hand-washing and for formula preparation, transport and emergency treatment. Incubators should be safe for use with oxygen. Medical and nursing records should be adequate.

These are, of course, the minimum requirements. When premature infants are cared for in a group, i.e., in a nursery, the danger of infection increases proportionally. It thus becomes necessary in a hospital plan to arrange to provide individualized, highly specialized care for each infant. Knowledge is insufficient today to select any particular type of care as so superior that it should be universally adopted. I do not mean that we do not know the general principles of care but only that there are alternatives for each one and very little exact information to help us choose between them.

Efforts to meet standards of facilities and technics have been accompanied by decreased mortality rates but they are not the only or the best criteria of good care. Morbidity, particularly in regard to asphyxia, birth injury and infection should be studied in relation

to different types of intrapartum, immediate postpartum and neonatal care. Subsequent mental, emotional and physical development needs to be related to early care.

Skilled nursing care and experienced clinicians provided with the minimum of equipment will save more premature infants than less skilled professional personnel with every modern type of equipment at their disposal.

The Expert Group pointed out that medical and nursing records should be adequate. Clinical charts of the day-to-day progress of the premature infant should be so set up as to guide the physician in the appraisal of the infant's progress. There should be nursing records also, arranged to enter, hourly, data on feeding, temperature, character and number of stools and any abnormal symptoms such as vomiting, cyanosis, convulsive seizures, jaundice and hemorrhage. In addition, the record forms should be so arranged that they may be used for statistical tabulation of data to facilitate evaluation of methods of care; to render reports to official agencies when asked for; and to increase knowledge of various aspects of prematurity such as incidence, mortality and morbidity rates, and causes of illness and death. The data should be analyzed in relation to birth weight and age. Special forms will obviously be required for special research studies.

Home Care

In many areas premature infant care will, by choice or by necessity, be given in the home but provisions for hospitalization of sick premature infants and of those in the lowest weight groups will be needed. One advantage of home care is that normal mother-infant relationships are promoted and the emotional needs of both mother and infant will be met more readily than under hospital conditions.

The Expert Group outlined the following minimum requirements for a home-care programme:

A. Adequate professional and auxiliary personnel, physicians to serve as medical advisers and consultants, public health nurses to appraise the suitability of the home, including the availability of proper facilities and equipment to carry out the parent-teaching programme, home helpers to enable the mother to readjust to domestic responsibilities;

B. facilities for transportation of staff and for infants requiring hospitalization;

C. adequate medical and nursing records;

D. arrangements for follow-up for medical care and assessment of physical and mental status.

Miller[7,8] has made two reports of a home care programme in Newcastle-upon-Tyne. Deliveries are conducted by midwives educated to appreciate the need for specialized nursing care of the infants provided by the Health Department. Of 220 premature infants born at home in the period 1945-47, the neonatal mortality rate among those "specialled" was 18% compared with a rate of 35% among those "not specialled." Later, Miller commented "it is quite apparent that the results of home nursing in Newcastle and admission to the hospital from the district in Birmingham are of the same order until we consider infants with a birth weight of less than 3½ pounds. Then there is a marked difference in favour of hospital admission. . . ." Miller urges the development of special units to which the smaller infants may be transported for care.

Educational Programmes

The expert group pointed out in each section of the report the importance of developing educational programmes not only for professional and nonprofessional personnel but also for the public and particularly for parents.

Parent-teaching should begin while the mother is in the hospital and be continued in the home by public health nurses or other qualified individuals. Such teaching is a requirement for a home-care program.

There is a need for development in some areas and expansion in others of training programmes for physicians, nurses and midwives in the specialized field of premature infant care. A country initiating a premature infant care programme should consider, as a prerequisite, a good general training for physicians, nurses and midwives, including pediatrics, obstetrics and public health.

Content of the specialized education programme should include:

A. Practical experience, under qualified direction and supervision, in a well-organized and equipped centre for premature infant care, with hospital, home and follow-up services;

B. instruction in and demonstration of generally accepted technics of premature infant care;

C. in-service training and frequent refresher courses for physicians, nurses, and midwives who are already engaged in premature infant care.

In order to promote team spirit, joint participation of both medical and nursing personnel for at least some of the period is desirable. The duration of the courses will depend on the individual needs of the professional group concerned. There is a great advantage if a team of a doctor and one or more nurses working in the same centre take the course together.

It was emphasized that there should be exchange of personnel, both medical and nursing, among centres for premature infant care within the country or from abroad. This applies directly to a new pilot project, for which it will be necessary to have the staff specially trained.

The Expert Group pointed out to national governments the desirability of considering the award of fellowships for research and study in order to promote progress in the knowledge of prematurity and the improvement of methods of care of the premature infant.

Research

The Expert Group, with full realization of the many gaps in current knowledge of all aspects of prematurity, did not consider it within its scope to present, in detail, specific research programmes. However, they presented examples of the types of research that are urgently needed:

A. The setting up, in selected areas, of study groups to correlate the gestation period with birth weight and other anthropometric as well as anatomic and physiologic criteria of prematurity. It is suggested that these investigations should take into consideration various weight groupings in relation to these other criteria;

B. a study of the nutritional status of pregnant women to determine the effects of malnutrition on prematurity. Studies previously reported have not been conclusive;

C. studies of the causes of premature birth; the need for such studies is indicated by the fact that in about half the cases of premature birth the causes are reported as unknown;

D. studies of the relation of social and economic factors to the incidence of premature births and deaths.

Information Service

Finally the Expert Group adopted the following resolution:

"The Expert Group on Prematurity

RECOMMENDS that WHO develop an information service on prematurity; such a service to include:

(a) collection of information on prematurity;

(b) compilation of such data;

(c) distribution of such information on request or through the medium of WHO publications;

(d) advisory service on sources of information."

The report of the Expert Group of Prematurity was adopted without change by the Third World Health Assembly, May 1950.

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SPECIAL REVIEWS

JOSEPH STOKES, JR., M.D., *Editor*

The following paper by Dr. Chapple is obviously a projection of his past thought and work into the future. It is to a large degree correlation and is also speculative. Data already obtained in pursuance of this working hypothesis will be published in the near future. Such combinations of correlation and speculation are often stimulating to workers in many fields and likewise to pediatricians.

AN INQUIRY INTO COMMON DENOMINATORS OF CELLULAR PHYSIOLOGY

By CHARLES C. CHAPPLE, M.D.
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INTRODUCTION

PHYSIOLOGIC function has been interpreted largely in terms of response to their inducing stimuli, and stimuli such as bacilli, viruses, heat waves, shocks or phenobarbital tablets, are expected to induce responses as different as the morphology of the etiologic agents themselves and each is considered to use a unique channel. But these channels are obscure. In general, drugs can rarely be found in the cells influenced by them, and micro-organisms often can be cultured only in local sites although central nervous system function, such as temperature control, is altered through their influence.

In this study, channels and mechanisms are sought which might be used by various stimuli. In the search, attention is paid more to common ground than to the acknowledged differences and specificities which are the more usual objectives of medical investigations.

This paper is an attempt to consider physiology from the standpoint of the cell, holding exogenous stimuli such as drugs, disease, psychic influences and irradiation to a role of secondary importance, while reviewing the extensive and normal endogenous alterations observable in blood pictures, growth patterns and elsewhere from conception throughout life.

* * *

Cells, the ultimate reactors, seem to have two states or, more accurately, phases. Each, for a time, is tense and then it becomes relaxed. These are familiar phenomena throughout the biologic world, and their very familiarity makes them seem too elemental for consideration. However, there is reason to believe that these regular alternations are of fundamental importance.

The relaxed phase of a cell permits its enlargement and its division into daughter

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cells. This is growth. The tense phase permits no growth, but instead solidifies and matures the expanded cell.

Such changes as occur in single cells are reflected in tissues. Normally these changes occur throughout the body in rhythmic alternations. Their cyclicity can be altered in amplitude or frequency by stimuli.

In the relaxed state, the entire molecular structure of the cell appears to be loosened. Chromosomes can separate from their counterparts in mitosis by what appears under the microscope to be almost a repulsion. The confining membrane loses its integrity and cell division occurs. Meanwhile, the permeability of the cell has increased and its electric resistance[1] has become high. Since nervous impulses are of electric nature, this cellular increase in resistance may be of assistance in accounting for the reduced response of the fatigued cell, or of the sleeping person; or of the concurrence of a state of mind with a physical state as exemplified by sleep and the muscular relaxation which regularly accompanies it. In the opposite phase, both cellular permeability and electric resistance are diminished.

The paper will discuss the apparent extent of such relationships of physical mechanisms and mental states in health and disease. This leads necessarily to speculation, so a further purpose of this paper will be to present a few tentative conclusions based upon these speculations and upon certain data already obtained.

The study was begun by the collection of facts established by investigators in several distinct fields and the concurrent application of these to anatomic fundamentals.

It might be characterized as a whole, borrowing from the terminology of labor unions, as a horizontal perspective, i.e., concerned with all the cells in all parts of the body simultaneously in contradistinction to the vertical approach of regarding the cell only in terms of its containing organ or system.

Since it is an attempt at another perspective, biologic processes in general can be considered by it. On this account, a variety of topics will be touched upon here, with no single topic exhaustively discussed, and the bibliography will be confined to a relatively short list of specific and pertinent papers although it could be several-fold this number.

In the future, data on the utilization of this perspective in the evaluation of drugs, the mechanism of their actions and similar subjects are to be published.

This is then, in a sense, a preliminary statement of a hypothesis and a presentation of the general nature of the data on which it is based.

Cellular Interdependency

As the study progressed, it seemed the inescapable conclusion that interrelationships and interdependencies extend throughout the body, that all physiologic functions are tightly interdependent; that each affects all the others and that the whole is mediated by the brain. John Donne's sermon upon the influence of one individual directly or indirectly upon all humanity describes a similar relationship of another order of magnitude.

Among the familiar anatomic interrelationships are these: Each cell has a blood and a nerve supply, each nerve a blood vessel, and each blood vessel a nerve. The wall of the blood vessel and the sheath of each fasciculus of each nerve are composed of the connective tissue which is also a major constituent of the skin, the sclera, the capsules of organs and glands and their internal and external supporting structure, the matrix of bone, the capsules and articular facets of joints, and elsewhere. This connective tissue or collagen

is modified in certain sites, but all these sites contain the physiologically responsive hyaluronic acid.

Since upon its integrity appears to lie the responsibility for such fundamental mechanisms as the ingress and egress of oxygen and of blood constituents of cellular, fluid, electrolytic and other natures, it would seem worth exploring the possibilities of altering this hyaluronic acid physiologically.

It is known that this substance, hyaluronic acid, is alterable in the skin. It may be assumed when alterations are induced there by general factors, that the hyaluronic acid in other locations must be quite as extensively altered at the same time. These alterations have been demonstrated as an increased or diminished permeability of the intercellular cement substance to various injected agents. The "spread" of injected dye can be increased by mixing with it hyaluronidase, the "spreading factor" of Duran-Reynals,[2] and the "spread" of bacteria and chemicals can be increased in the same manner. This observation has been put to clinical use in expediting the absorption of injected fluids.

The spread of dye can be extended beyond the limits of a local hyaluronidase effect, however, by the administration of progesterone, and it can be limited by estrogen. This observation was made by Lurie.[3] In one experiment, Lurie exposed rabbits to inhalations of atomized cultures of tubercle bacilli. Certain of the rabbits had received estrogen prior to their exposure; others received progesterone which had been preceded by administration of pituitary gonadotropic hormone. In those rabbits which had received estrogen, the dye would not spread on intradermal injection, and these rabbits also resisted infection by the tubercle bacilli. In the progesterone-treated rabbits the dye spread widely as did the infection. On this evidence it seems reasonable to assume that permeability of tissue may be related to its hyaluronic acid content and be dependent upon its state and that this state might constitute an essential part of the obscure mechanisms known as resistance and susceptibility to infectious disease.

Another common denominator among cells is blood. This substance is an aggregate of cells, fluids, electrolytes, nutritive elements, end-products and other components, most of which are obtained from sources outside the blood vessel walls and must pass through the walls at their destination. Certain of these constituents are manufactured by organs, glands and other parts within the body. If these suppliers vary in the quantity or quality of their products, this variance is reflected in the blood and, conversely, any alteration in these components of the blood is the result of change in those manufacturing body parts, while the vessel wall's permeability remains the same.

Because of these physical and chemical common factors, it seems evident that a change in a blood vessel must inevitably result in a change in a nerve, and vice versa. For example, essential hypertension is a condition so designated because blood pressure can be measured more readily than can nerve response. But, the effects of prolonged hypoxia associated with hypertension on the peripheral and central nervous system often become the predominant manifestations and are evident to a degree from the start. Perhaps the nervous element may even be primary. It is difficult to detect the point at which a circle is started.

The magnitude of alterations in blood vessels and nerves must vary widely, and the magnitude of the changes induced by them must, in turn, vary with the nature of the stimulus, the type of cell on which the influence is exerted, and the directness or proximity of that influence. For example: a burn on a finger injures the skin locally much more severely than it affects kidney function, but kidney function probably is altered nevertheless, since it is demonstrably affected in severe burns.

In summary, cellular anatomic interdependency is extensive. Blood vessels, nerves and all intercellular cement have in common hyaluronic acid. The state of this substance can be altered by normally circulating hormones and may influence the permeability of cells in general to oxygen and other blood constituents as well as to bacteria.

Drugs, Disease and Hormonal Interrelationships

Because of the important roles played by the so-called female sex hormones, estrogen and progesterone, in the "spread" it seemed advisable to compile available information on their other influences. This compilation showed the hormones of the adrenal to be closely interrelated with estrogen and progesterone. Then, because these interrelationships suggested that there might be others of equal importance, it was decided to include hormones of all the endocrine glands in the survey. Selye's text[4] was found to include more detailed information than any other single source, but the search was by no means confined to his works.

It soon became apparent that interrelationships among the endocrine glands are quite as close and as extensive as those of nerve, vessel and blood. Furthermore, the mode of action of hormones suggests a similarity to the mechanism of action of drugs and disease, of growth, maturation and age.

The importance of endocrine influences can be estimated in the example already given, i.e., the ability of estrogen and progesterone to alter the resistance of the intercellular cement substance to the spread of dye or to inhaled tubercle bacilli. These hormones circulate normally in all individuals, but it is not these hormones alone which affect this faculty of collagen. The adrenal hormones, too,[5,6] and drugs such as salicylates,[7] have been shown to influence "spread." Besides these, age, sex and state of health have been related to absorption and "spread" in the McClure-Aldrich test,[8,9] in which the disappearance of injected intradermal saline is observed.

Each of these factors influencing "spread" may act in an individual channel, but it is at least equally possible that more than one act through the same channel and by the same mechanism. Certainly, drugs, disease, age and sex may be assumed quite as logically to affect the endocrine interrelationships primarily and to alter the intercellular cement substance as a result as to assume that they strike this substance directly.

Certain endocrine influences affect all body components as is clear in the case of the thyroid. This gland is recognized as being instrumental in the regulation of the metabolism of all cells, and these must include the cells of the other endocrine glands. Thyroid stimulation is accompanied by an increase in certain hormones and a diminution in others. Conversely, other hormones are capable of modifying the thyroid's activity. The close integration of the secretion of this gland with those of others can be illustrated by the regular variation in thyroid activity with estrogen and progesterone. The excretion of these hormones is minimal at the time of the menses and their excretion pattern is generally assumed to parallel their blood levels. At this time the thyroid enlarges, becomes tender, and assimilates little iodine, and the menstrual blood becomes high in this element. The basal metabolic rate declines and the body temperature falls. These facts might suggest that the thyroid initiates menstruation but it cannot be determined on this evidence alone which, if either, the thyroid or the gonad, is the primary instigator of the process.

Another type of example of interglandular influence is found in the study of a single physiologic phenomenon, such as the calcification of bone or the concentration of glucose in the blood.

In the case of calcification, the parathyroids are usually allowed to assume full glandular responsibility, but the thyroid, the adrenal, the pancreas, the pituitary and the gonads have all, in independent studies, been shown to affect it. In the case of the circulating glucose, it is ordinarily the pancreas which is held fully accountable, and though the influences of the other glands on this list are recognized they are usually considered to be inoperative under normal circumstances.

This implies reluctance on the part of the other hormones, except under exaggerated conditions, to participate in mechanisms within their provinces, but it would seem as probable that these various endocrines operate normally in the control of glucose metabolism, or calcification of bone, and that under exaggerated conditions their roles are simply more apparent.

If a hormone is observed to participate in one physiologic phenomenon, would it not be reasonable to assume that it affects all the other cells and functions within its sphere of influence at the same time? If so, it would seem important to know the extent of this sphere.

In this attempt to determine the breadth of action previously observed for various hormones, examples of responsiveness of cells, tissues or functions to more than one hormone, were discernible. Admittedly, any such compilation of data from a rapidly expanding field must be incomplete, but the study was sufficiently comprehensive to suggest that a total interdependency exists among the endocrine glands, and that an alteration in the secretion of any one hormone influences all the others and, as a result, each directly or indirectly affects the entire body. As a corollary to this, a stimulus to any part must be reflected throughout the entire body.

Published observations of hormonal activities were collected and tabulated as a graph. On the ordinate were listed the hormones studied, and on the abscissa the physiologic functions which had been observed to be altered by the administration of each or, conversely, by extirpation of the gland secreting it. At each point a bar indicated the direction and degree of the altered function by the length of its extension above or below a median line. The number of observations recorded on the abscissa must be lower than the total number reported in the literature, but it was a surprisingly high figure, being well over 300. No one hormone had been studied in all these functions but certain hormones had been observed in a considerable number of them. With the exception of the thyroid gland whose general influence has been commented on, the pituitary influence was the most ubiquitous, as might have been expected.

Aside from the hormones of the thyroid and pituitary, those observed as having by far the most widespread influence over the body were the so-called "female sex hormones," estrogen and progesterone. These had been noted as influencing 113 and 63 physiologic functions, respectively, aside from the approximately 70 studied in the reproductive system. Their influence had been noted on electrolytes and metabolites, upon cells, tissues and functions, and upon states of mind and behavior. The last named were not included as physiologic activities, nor counted in the numbers mentioned. The studies of these hormones collected from the literature had not been confined to man but included observations on birds and animals as well. Both sexes were observed, especially in the case of estrogen, since this hormone had been shown by Zondek[10] to be in higher concentration in the males of at least certain species than in the females.

The influence of these hormones has been observed so extensively that the impression is gained that their scope is as encompassing as that of the thyroid's secretion. If these

hormones have been labeled correctly as sex hormones and still affect so many fundamental physical and mental processes, it suggests that reproduction is dependent upon growth and health as well as upon sexual activity and that the mental attitude is not too dissociated from the process. It suggests, in short, that sex, psyche and soma are an indissoluble trinity.

The nature and extent of the influence of these hormones might be illustrated by some examples. Estrogen and progesterone appear to be physiologic reciprocators or antagonists of each other. There is some evidence in each of the following situations: Estrogen stimulates mental and physical activity; progesterone is a general anesthetic. Estrogen induces positive and progesterone negative balances of nitrogen and calcium. Estrogen increases urinary output; progesterone diminishes it. Estrogen opposes water retention of tissues; progesterone favors it. Estrogen facilitates pigmentation; progesterone pales it. Estrogen promotes calcification of bone; progesterone promotes an increase in formation of cartilage. Estrogen prevents hair growth on the face, trunk and extremities; progesterone stimulates it. Estrogen induces vasco-constriction; progesterone, vaso-dilation. Estrogen reduces lymphatic tissue including the thymus and the number of circulating lymphocytes; progesterone increases them. Estrogen toughens the mucous membrane of the vagina and the mouth; progesterone softens it. Estrogen increases the tone of connective tissue; progesterone relaxes it. Estrogen reduces the spread of an injected dye; progesterone increases it. In these functions and in many others their influences appear to be opposed.

Although the reciprocating action of these hormones is less clear in another field, it is evident that bleeding, clotting, sedimentation and prothrombin times vary regularly during a menstrual month and in pregnancy with the amounts of these hormones circulated.

These assorted functions would suggest that each of these hormones has numerous separate effects, but this does not appear to be the case. Instead, all the effects of estrogen appear to have one common denominator, and those of progesterone another.

Their apparent versatility is similar to that of thyroxin which is so familiar. This hormone elevates the BMR and the body temperature, calcifies epiphysial centers of bone and dentine of teeth, atrophies muscle and reduces its creatine, diminishes glycogen storage, lowers blood concentrations of cholesterol, decreases the excretion of urea and creatinine, and increases calcium and phosphate excretion. Despite these diverse expressions of thyroxin's influence it is not felt that it is a hormone of varied capabilities, but that each manifestation can be explained on the basis of alteration of the metabolism of the cells involved.

In the cases of progesterone and estrogen explanations which parallel that describing the thyroid's activity appear to be equally satisfactory. If the thyroid were to be considered a governor, as it often is, the function governed is the speed of utilization of metabolites. The thyroid then might be considered the physiologic equivalent of an accelerator. Estrogen, considered similarly, would seem to govern intensity, or energy. Its equivalent in an engine would be the spark. Progesterone appears capable of conducting away or dissipating that intensity as in the grounding side of a circuit, together they seem to constitute the ignition system.

Estrogen's effects are remarkably like those of a brisk, bright morning; progesterone's those of the afternoon heat, and the two seem as clearly to alternate. In terms of the individual, estrogen is accompanied by alacrity and responsiveness; progesterone by

relaxation and sleep. In terms of organs and tissues, estrogen is associated with tonicity and rigidity, progesterone with flaccidity and fluidity; in terms of cells, estrogen stimulates compactness, progesterone allows looseness, enlargement and division. In short, progesterone promotes cellular multiplication or growth, while estrogen, in turn, appears to consolidate the gains of that growth.

* * *

Multiple glandular influences have been observed widely. Since the thyroid's influence is ubiquitous, it must be assumed that wherever a gonadal hormone's effect has been noted, it is in addition to the effect of the thyroid. This probably is no less true of the effects of other glands; the adrenal, for instance. This much studied gland can alter the speed and the timing of the cellular engine in either direction and can reinforce the intensity, either toward energy or relaxation, by its medullary or cortical factors.

It is conceivable that the adrenal does no more than this. It has definite effects on musculature, on the calcification of bone (it has been demonstrated by DeBosányi[11] that epinephrine, plus hemoglobin, will heal rickets in rats), on hyaluronic acid,[5,6] and on the manufacture of blood cells.[12] Because of its effect on the circulating blood, if for no other reason, it must affect all cells of the body, but there is no evidence that it acts directly on each cell. On the other hand, the adrenal may affect each cell directly and estrogen or thyroxin act only through influence on the adrenal.

Certainly the sex hormones influence the adrenal strikingly. Their interrelationship is especially vivid in the newborn infant who has been swallowing, inhaling and generally absorbing a medium high in these steroids. In the newborn, the adrenal gland is huge and the genitalia are enlarged. This can be demonstrated also in adult animals in laboratory experimentation in which, for example, the administration of estrogenic substances is followed by cortical hypertrophy.[13] The adrenal's effect on the gonads is quite as striking, as is noted, for example, in the pseudohermaphroditism of the adrenogenital syndrome; or in the ovarian enlargement following adrenalectomy in rabbits.[14] This raises some interesting questions. Is one gland capable of initiating activity which is detrimental to another, or is the subsidence of activity of one gland stimulatory to its physiologic antagonist? Or are, more logically, all glands under common control and as incapable of overwhelming one another on their own initiative as the right hand is the left? Further, do exogenous stimuli such as drugs and disease simply upset a hormonal balance and thereby affect all cells?

Glandular Anatomy in Relation to Glandular Physiology

The embryologic origins and the anatomic characteristics of the endocrine glands are different and therefore suggest differences in their modes of action. The adrenal appears to be about the mid-point of the pattern. This gland arises about equally from nervous and somatic tissues. Its chromaffin originates as part of the central nervous system and is most incompletely separated from it during the lengthening of the fetus. As it is stretched apart, bits are left as carotid and accessory chromaffin bodies. This chromaffin because of its origin and the speed of its action must be assumed to have nervous components as well as the chemical constituents which currently are being so thoroughly investigated. The electric and nervous elements of the adrenal may initiate sudden actions, while the chemical components stimulate prolonged action.

This same mixture of chemical and nervous elements seems to exist even more clearly

in the pituitary. This gland, in the mechanical analogy, can be considered as no more than the robot-pilot and probably it is only a switch-board through which the true robot-pilot transmits its impulses to the soma. The robot-pilot itself would seem to be those parts of the brain concerned with involuntary functions, the cerebellum and all that not engaged in sensory or voluntary mediations. From here, messages can be transmitted via the hypothalamus to the pituitary that this or that manufacturing gland should extend itself or relax.

The purely somatic endocrines have greater chemical than nervous components, and as these glands ascend the nervous scale and become more closely associated with the brain the proportion reverses itself. When the adrenal is compared to the thyroid the nervous elements are considerably greater in the former. In the pituitary they are greater than in the adrenal and in the hypothalamus no chemical manufacturing whatever seems to go on. A hypothalamic secretion will probably be detected in the future,* however, since electric changes induce chemical changes and the two phenomena are indissoluble.

On a strictly morphologic basis, it would be incongruous to assume that the pituitary functions were on the same basis as those of somatic endocrines. The pituitary has 20 odd stimulatory functions. The somatic glands, each manufacturing appreciably fewer hormones, are physically impressively larger than the pituitary. It is equally incongruous on a physiologic basis. The pituitary's blood supply is remarkably meager for a gland which delivers great quantities of hormones by this route. Its nervous connections, however, are substantial in that the gland is connected directly via the optic chiasm, anteriorly, to the corpus callosum and, posteriorly, to the peduncle atop the spinal cord. In such a critical site between the brain and the spinal cord it seems likely that it is a way-station, a translator and a transmitter of brain impulses to the body. This seems the more probable in light of the discoveries in the hypothalamus of "seats of control" which had formerly been thought to be situated in the pituitary.

In any case, it is only logical that to this tiny gland should not be attributed the powers of judgment on the degree of attractiveness of a member of the opposite sex, nor the ability to decide in any situation whether or not to order out the adrenaline. It seems quite unlikely that it can sense the need for pancreatic activity and the like, although it can stimulate glandular activity reflexly. The same must be true regarding the ability of the hypothalamus to decide upon the fatigue and circumstances for sleep. It seems logical then that higher centers must initiate the hypothalamic and the pituitary impulses.

If one pursues the mechanical analogy previously used, the automatic brain may be the robot-pilot but utilizes the same driving mechanism as the rational brain. The brain has no counterpart in the engine but, of course, is the driver. This organ is comprised of cells in which the nervous, or electric, elements predominate to the exclusion of recognized chemical factors. These cells are the ultimate of the electric components in the inverse proportion which seems to exist between the nervous and the chemical factors of the body.

The thyroid might appear to be at the other end of the scale, with its large chemical and small nervous components, but there is reason to speculate that completely somatic cells, such as those of the skin, may be the brain cells' opposites and be capable of efferent chemical stimulation. A circumscribed area of skin exposed to ultraviolet induces calci-

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* Since the writing of this section, such a hormone has been identified by Hume and Whittenstein.[16]

fication of bone, and local pigmentation of skin after local edema and/or vasodilatation. Each of these separate effects has been observed to follow the selective administration of estrogen or progesterone.

To this point the discussion has been concerned with anatomic interrelationships and interdependencies, and with observations and speculations upon controlling mechanisms. The following section will consider the cyclicities which have been observed, again by a number of investigators, in body functions.

Cyclicities of Body Functions

The thyroid has no apparent specific antagonist to its thyroxin. When the accelerator, thyroxin, is decreased the cellular metabolism is slowed only in degree. With estrogen and progesterone on the other hand, there is a reciprocal action when there is a reduction of the original activity. Either the one or the other hormone apparently is in relative predominance at every moment.

This action is much like a thermostat on a pleasant, cool day, which turns on the furnace (estrogen) to raise the room temperature, and having raised it enthusiastically too high, turns on the cooling system (progesterone) to reduce it and then repeats the process. Of course, the hotter the furnace heats the room, the more cooling will be required to reduce the temperature, but since it is a cool day and the normal state of the room is cool, its tendency is to return to and remain in that state. Under these circumstances it is probable that no true equilibrium can ever be attained, but each phase will remain dependent upon the intensity with which it was applied. This analogy is to suggest that on the cessation of the effects of estrogen the progesterone influence predominates.

Another analogy is the comparison of estrogen to the electric intensity collected in a Leyden jar, the body, and progesterone to a flame which can discharge it. Normally the jar receives charges of varying intensities which are discharged by the flame. Large surges fill the jar to capacity, as do repeated small stimuli between the intervals of application of the flame. When the jar is filled its tendency is to empty itself by leaking, if complete discharge by heat is not immediately forthcoming. When the jar is empty it has no tendency to refill itself but has the capacity to be filled when the electric energy to fill it becomes available. In the body intensive activity demands rest, but rest does not demand to be followed by intensive activity, although the capacity for activity is restored.

Alternation between hormonal predominances, or at least between the effects observed as being their concomitants, is evident in many ways. A few examples of the influence of estrogen are mental activity, muscular alacrity, urinary excretion and a reduced number of circulating lymphocytes. Examples of the influence of progesterone are mental languor, muscular relaxation, diminished urinary excretion* and an increased number of circulating lymphocytes. It is evident that these groups of functions alternate with a remarkable regularity in terms of a 24 hour day. With them vary the electric resistance of the skin, the Addis counts,[17] and in animals at least,[18] alternation of calcification of bone with bone growth and the number of mitotic figures in biopsies of normal tissues in both animals and man.

To trace a 24 hour day in terms of the familiar, sleep and consciousness can be con-

* Probably on the basis of normal blood flow with greater tubular resorption as shown by Sirota, Baldwin and Villarreal[19] to be the case at night.

trasted at once; then the activity of the mid-morning can be compared to the lassitude and relaxation which follows meals. In this connection it will be recalled that there is a lymphocytosis following meals which may exceed that which occurs during a night's sleep. But even without a meal the differential count tends to change in the same direction after the usual meal time.

Such alternations as these cannot be considered to be controlled exclusively by progesterone and estrogen. The adrenal's and the thyroid's fluctuation with estrogen have already been commented upon, so it is not conceivable that a change in the amount of circulating estrogen and progesterone can be a change in these two hormones only and undoubtedly the same fluctuations could have been correlated with states of adrenal activity.

The fluctuations of estrogen and progesterone are obvious in terms of a month and the fluctuations in the activity of the thyroid and the pituitary become evident in this longer interval as noted, for example, in gonadotropin excretion. Since there are monthly fluctuations in the case of the pituitary and since the pituitary appears to be a way-station of the central nervous system perhaps it should be more correct to state that, during longer observational periods, fluctuations become evident in the intensity or energy of the central nervous system.

The many fluctuations observed in physiologic activity all have an evident rhythmicity. The most widely recognized as periodic is menstruation, but there are both longer and shorter cycles. They vary from a fraction of a second to years in phase. The shortest are brain waves and nerve impulses, and the cycles increase in phase through cardiac impulses, inspiration and expiration, hunger and languor, consciousness and sleep, growth and maturation. This progression can be visualized best as a kymographic record of respiration which would include the smaller variations registered by the cardiac impulses, and which if they could be so recorded, would show the minute nerve impulses reaching the heart.

There is a possibility that all these rhythms originate physiologically in the brain where, in their highest frequencies, they are the brain waves. These, not being insulated from the rest of the body, cannot be assumed to be confined to the central nervous system. Instead, they appear to be collected, as if in condensors which discharge them periodically, according to the capacitance of each, proceeding in harmonic progression from the brain, to the heart, to respiration and further.

Afferent impulses to actuate the heart would be collected until sufficient intensity had been reached to contract the organ. Then the intensity would be conducted to the respiratory mechanism, where it would be again collected until it could empower inspiration and again the process be repeated in each of the succeedingly larger condensors.

The number of components involved in the rhythms ascends rapidly until all the body is included. Each rhythm appears capable of reaching maxima varying with, and dependent upon, different stimuli. The rhythms of highest frequencies and shortest phase are best recognized electrically; those of the intermediate range, chemically; those of the long phases, clinically.

This alternation between tense and relaxed states is evident in rhythms of high frequencies, such as nerve impulse and the cardiac systole and diastole. In waves involving the entire body, the most striking example of its existence is to be found in sexual activity. Here the increase in mental and physical intensity reaches a high maximum and

is followed by a pronounced mental and physical relaxation. Less conspicuous reciprocal responses might be expected with maxima of lesser degree.

The short and intermediate phase waves have so far been mentioned largely to identify them as waves. Longer phases than those observed in the 24 hour day are the weekly period of relaxation, recognized physiologically, and religiously by the Sabbath. The biweekly period is demonstrable in temperature fluctuation and hormone excretion patterns as well as in the regular variations of energy and relative depression. The 28 day period so familiar in women requires no comment and there is some evidence that a similar cycle exists in males.

Longer phases permit the recognition of other physiologic variations which are less evident during the shorter intervals. For example, on a biweekly basis and more strikingly during the phase of the lunar month, there is a regular variation in the patterns of the circulating proteins, electrolytes and fluids and in the sedimentation rate of blood and its differential cell count, in bleeding, clotting and prothrombin times, as well as in other physiologic phenomena including mental and physical vigor.

The seasons induce physiologic responses regularly. Growth in children is faster in the spring and early summer than during the rest of the year, while their weight increases more rapidly in the fall and winter. It is of interest that Malling-Hansen[19] showed diurnal variation in weight and height to be on the same curve as those of the other diurnal changes.

The longest of all physiologic cycles is the most familiar one, commonly known as the life cycle, with its growth phase beginning at conception and ending during adolescence, to be followed by the consolidation of that growth which will continue for the rest of the life span, at first beneficially and later detrimentally, but without directional change. Within this great cycle of man's life lie all the lesser cycles and the greatest of these conditions the lesser ones, just as each of the lesser ones can condition its lessers. Conversely, the intensity of the least of the waves can affect the greatest of them.

As part of this great cycle is one which itself increases progressively in both the length of its phase and its intensity. This cycle becomes evident shortly after conception and can be followed on the basis of changes in the blood, in growth rates, in susceptibilities to diseases, and in other phenomena throughout the span of life.

In each phase, extrinsic stimuli may alter the frequency or amplitude of the rhythm. In the absence of extrinsic stimulation a course of rhythmic alternation is pursued between expansion and contraction, relaxation and tension, growth and consolidation of that growth. Change in the amplitude or frequency of the rhythm apparently can be induced by such extrinsic stimuli as sound, electricity, light, temperature, radiation, vitamins, minerals, foods, drugs, psychic factors, trauma, and infections, gases, odors, toxins, temperature changes, allergens and perhaps taste.

Examples of Stimuli Affecting Physiologic Cycles

Random examples from the list of stimuli may illustrate their abilities to stimulate hormones or otherwise alter the normal rhythm:

1. The most obvious is electricity itself, which in mild degree causes muscle contraction, in moderate degree, convulsions, and in severe degree, blood coagulation and death. Nonfatal electric shocks are followed by a proportionate relaxation. This is evident physically and mentally and it stimulates other discharges of intensity.

2. Vitamins are substances of potent biologic activity which are prescribed only negatively, i.e., not for an intrinsic benefit, but only for the remedy or prevention of a deficiency. Yet, each vitamin was originally obtained from a plant or animal which utilized it as a stimulator of growth or consolidation, but not of both. Vitamin B, for example, is a stimulant of cell division and vitamin D induces consolidation of growth even when no deficiency exists. Clinically, the ability of these vitamins to alter the normal cycles becomes especially important in infants or postmenopausal individuals, since these groups theoretically are less capable of compensating for gross imbalances either toward stimulation of growth or of consolidation. The vitamins may use the channels of hormone stimulation. This is suggested by the Silberbergs'[20] success with estrogen in the prevention of scurvy and its alleviation in a vitamin C-like manner in guinea pigs, by the similarity of the action of estrogen and vitamin D on bone, the resemblance of progesterone's effects to those of vitamin A on epithelial and bone growth, to the vitamin B complex on epithelium and connective tissue and to vitamin E on blood cholesterol, lipids and the development of the amniotic cavity.

3. Coal tar, an example of drugs, induces estrus in mice[21] and aspirin diminishes "spreading,"[7] both functions of estrogen.

Antibiotics have been regarded as affecting only the invading organisms, but certain antibiotics have been shown to affect calcification of the bone,[22] growth,[23] or the bleeding and clotting times of the host.[24,25] These are not local effects. Their action on bacteria may be accomplished through an ability to start the consolidative phase in the micro-organism,* or they may alter the accessibility of the host to the micro-organism through alteration of his general status, particularly altering the host's phases of permeability and impermeability.

4. Allergens should be discussed in brief in this connection. The common allergens, milk, eggs, wheat, ragweed pollen and many others are derived from the reproductive systems of plants and animals and on this account might be assumed to be high in "sex hormones," or to designate them differently, in factors capable of altering permeability, electrolyte and fluid balance and the other characteristics of either the tense or the relaxed phase. This assumption would seem to be substantiated by the fact that the most prolific and rapidly growing plants are often the worst offenders as allergens. Investigation along these channels has not been extensive, but estrogen was found by Ascheim[21] in the pollens he examined and, of course, seeds,[27] milk[28] and eggs[29] are known to contain it. Muscle meats and plant stalks would be expected to contain relatively little of these factors, but blood and sap may carry appreciable quantities of them.

Since clotting phenomena vary regularly with the circulating hormones the hormone quantities might be considered as factors in transfusion reactions. The early stage of clot-

* Indeed there is no satisfactory explanation for the mechanism of action of antibiotics on bacteria *in vitro*. Bacteriologic technics cannot determine life or death in micro-organisms, but only establish their capability or incapability of growth. Even the absence of oxygen utilization cannot be accepted as proof of death since dormant seeds of plants can sprout after extended periods of anoxia. In addition, bacteria which were thought to be killed by ultraviolet light, a known stimulator of the consolidative phase, have been shown to grow at a later time on exposure to visible light.[26] The same phenomenon has been observed with certain "bactericides" in a few experiments.[25] It would appear then that antibiotics and bactericides may differ only in magnitude. Bactericides attack the host so heartily that they cause more harm than good, while antibiotics have a moderate or beneficial degree of activity in the host although they are capable of deterring the growth of bacteria.

ting is agglutination, and on this account the hormonal balance may influence blood grouping phenomena as well.

5. Startling noises interrupt the respiratory rhythm of the newborn infant and cannot be considered to reach him on a previously established emotional basis. Lullabies are as effective in an opposite direction. In individuals of all ages, dirges, martial music and rhumbas induce different responses. Definite effects of sound have been noted in animals, and composure can be alternated with states of excitement by changing sound frequencies.

6. Odors can repel or attract, even if not as greatly as the perfume advertisements suggest. Sharp odors check respiration as abruptly as do startling noises. The potent odors are, again, largely from the reproductive systems of plants or animals and commercially they are concentrated in bases from this system.

7. Radiation, like some of these other examples, is deserving of more than casual listing, but only its high spots can be considered here. The term properly defined includes all the electromagnetic radiations which begin with cosmic rays, proceed by increasing wave lengths and diminishing frequencies through gamma rays, x-rays and ultraviolet light before reaching the visible spectrum. As they further increase in length and diminish in frequency, they encompass the visible spectrum and infra-red, and progress through radio and power transmission waves.

The shorter waves, those below the visible spectrum, all appear capable of inducing the consolidative or maturing phase primarily. Ultraviolet light, for example, stimulates pigmentation and calcification of bone. The redness and edema of the skin in sunburn do not accompany the inducing exposure but are the secondary effects which follow in the compensating phase. On their subsidence, the consolidative phase resumes and pigmentation appears. This suggests that the phases induced by ultraviolet are to be measured in hours.

X-ray induces a longer consolidative or maturation phase which is followed at a longer interval by a less conspicuous back-swing growth phase. In the presence of acute inflammation the back-swing may be evident within 24 hours which suggests that the phase of x-ray is to be measured in days. Radium induces a still longer phase. Burns from it remain consolidative, without adequate epithelial proliferation for years before the back-swing, but then the growth stimulus reappears.

Infra-red radiation, on the opposite side of the visible spectrum, stirs growth first before consolidation. Radio waves, the next in order of ascending length and the shorter waves, the cosmic waves below the gamma frequency, are known to be effective but in nature have not been shown to have definite physiologic import. These and the gamma and x-rays reach the body in exceedingly moderate dosages. Intensive exposure of the biologic world is limited to the band from ultraviolet through the visible spectrum through infra-red.

This critical band to which the biologic world is regularly exposed induces cellular maturation at the ultraviolet and favors cellular growth at the infra-red in their initial stimulatory effects. The mid-point of this band is, curiously, neutral green. Yellow green is on the growth side and dark green on the maturation side of the spectrum. These variations of green, so familiar in the growing yellow-green of plants and the dark green of the mature leaf suggest that chlorophyll may be a particularly responsive agent to electric field variation and that it may translate these variations in the same general fashion in plants that other chemical translators appear to accomplish in man.

8. Psychic factors are responses to stimuli originating within the imagination or transmitted to the brain by one of the special senses. Their effect on the soma, however, is as definite as if they had been induced by drug or disease and apparently the mechanism for production of their effects is the same. They alter the body sufficiently to alter blood counts, as the difference between two needle pricks a few minutes apart in an infant shows. They appear to alter permeability as the appearance of ulcers in the intense individual suggests. These examples are those of exaggerated responses, but the improvement in digestion with peace of mind is familiar, and there are countless similar examples. That psychic states affect the phases of growth and maturation can be illustrated by the failure of the psychically disturbed to reach full growth. To state it conversely, by the continuous intensification of their consolidative phase, psychically disturbed children become "psycho-somatic dwarfs."

9. Hormones, when administered, although not properly extrinsic stimuli, are exogenous for the individual. They act to a more intensive degree than do the individual's own, by virtue of their quantity. Since this is obvious, they are mentioned here only to draw ACTH into the discussion for a moment. This hormone, like the others from the pituitary, stimulates the activity of the more somatic endocrines. Its continued administration can prolong the phase stimulated, and perhaps its amplitude, but reciprocal action must logically be expected on withdrawal or on achieving the level at which the estrogen-progesterone relation must reverse itself.

Each of the above examples is capable of affecting the rhythms of the individual through a general stimulus even though it be applied to a specific part as in the case of an odor to the nose, or the needle prick to the skin. Each may be exerted more directly upon one part than another (specificity), but the response induced in one part must be reported to the brain and so be reflected elsewhere throughout the body.

Certain of the more obvious aspects of the life cycle will be described next. In describing this cycle where a predominating hormone is mentioned, it is understood that all other hormones and the physiologic states are unavoidable and simultaneously affected.

Natural Phases of the Life Cycle

Fertilization starts the life cycle. Spermatozoa are delivered ordinarily at the climax of an intensive state. One sperm penetrates the ovum during a permeable phase. The permeability of the ovum is probably dependent on the mother's physiologic state since she now has a corpus luteum. This debatable point may be of some interest in connection with the relative infertility of the psychologically intense. Although it is commonly assumed that the sperm penetrates regardless of the state of permeability of the ovum because of the presence of the "spreading factor" in the sperm, it seems probable that both mechanisms work in conjunction.

Following fertilization, the egg becomes capable of implantation, a process impossible for unfertilized eggs. This change in the reception accorded the egg may be because it now bears the spermatic faculty of penetration of the contained sperm, and in addition the implantation may be facilitated by the luteal effect on the permeability of endometrium.

In any case, it seems clear that the luteal influence on the new embryo is real since the latter can be readily damaged by certain virus infection during the first trimester. This is as long as the influence of the corpus luteum persists as is shown by the fact that ovariectomy subsequent to this time does not alter the course of pregnancy.

During the second half of the gestational period, the mother's excretion level of estrogen climbs and is followed by a rise in her progesterone excretion. At term the progesterone level falls alone and with the departure of this fluid accumulator and muscle relaxer, comes labor. Meanwhile, the fetal blood count gives evidence that the fetus has been subjected to the same hormonal influences.[30] (The fall in the maternal progesterone may not have occurred at the time of elective cesarians which may explain the greater quantities of intratracheal fluid often found in these infants.)

Since cellular division is stimulated by progesterone, a large exogenous supply of this hormone might be expected to induce an increase in blood cells, as well as in other cells. The blood count of the newborn infant has a higher number of red and white cells than is normal at any subsequent time of life. As supportive evidence there is a lymphocytosis in early fetal blood counts which has probably been present during the entire progesterone phase, but when the relative predomination of estrogen appears during the second half of pregnancy the lymphocytes are suppressed and the polymorphonuclear leukocytes predominate in the blood picture.

Further evidence of alterations and increase of the influence of the accumulating hormones is found in the pigmentation of the Negro infant. The hair becomes pigmented at about the fourth, and the skin during the seventh or eighth fetal month. This periodic increase in pigmentation is noticeable in white children as well, but in less degree. The blue eyes of a white infant which are destined to become dark become so with his first rise of endogenous hormones after birth, but his hair which is often dark when he is born can become blonde during childhood and does not darken appreciably until the later and more vigorous rises, especially at puberty.

There are many other reasons to support the belief that the hormonal effects on the fetus are important. The disproportionate size of the uterus, the enlargement of the clitoris and labia minora of the female occur regularly, and the size of the adrenal and liver in both sexes. The enlargement of the liver at this time and its persistence during the period of infancy calls attention to the chemical similarity between the hormones and bile. It suggests that the liver may be an instrumental site of conversion of hormones for excretion and even of their manufacture. Furthermore, there is a morphologic similarity between the organizing corpus luteum and the liver lobule. This resemblance may be only superficial but since the hormonal sources are definitely not limited to the gonads, it seems worthy of mention.

By following the infant in health and disease, and by correlating his states with an estrogen-progesterone relationship, it is conceivable that clues may be found toward the solution of problems pertaining to all ages. For example, when the excretion of these hormones is altered, the clotting of the blood is altered concurrently. In the newborn infant, while the hormonal concomitants are strikingly high, blood is anticomplementary; blood grouping is not well established. Some clues may be found also for susceptibility and resistance to infectious disease. Diseases appear to vary in a manner which cannot be explained totally by immunology. Certain large epidemics[31-38] have had universal patterns when divided into age increments, whether the incidence is studied in terms of morbidity or of mortality, but it is logical that these two should not be at great variance since they are different only in expressing degrees of susceptibility and resistance. For example, the pandemic reported in the Faroe Islands by Panum is often quoted as proof that all individuals are susceptible to measles when they have not been previously

infected. This implies that all are equally susceptible. However, the report shows quite clearly that the threshold for admission of infection is low but that in certain age groups, those infected were made only slightly ill while in others, many died. Additionally, it appears that the mortality curves on an age basis simulate the morbidity curve of other epidemics of less severity. The patterns for all diseases should theoretically be the same, that is, the greatest susceptibility should be expected in infancy and then after repeated subclinical attacks and exposures, the resistance should increase with age. But this does not seem to hold true for all and, in fact, it appears to be fairly sharply limited to those diseases which have a high polymorphonuclear blood picture.[31, 36, 37] On the other hand, those infectious diseases with a relative lymphocytosis such as mumps, typhoid and measles have a pattern of increasing incidence throughout childhood[32–34] during the time the first group is diminishing in incidence. It is not intended that these apparent facts should be interpreted as an attempt to cast doubt on recognized immunologic facts, on specific immunity, or transfer and development of specific immunities, but the existence of these patterns should be recognized and they should be considered in problems not now fully solved.

The hydration of the newborn infant, his blood picture and the relaxation of his stretched joint capsules all change gradually over the next few days and, of course, coincidentally his meconium diminishes. It is logical to expect meconium, the remnant of ingested amniotic fluid, to be a hormonal reserve of both estrogen and progesterone for the infant.

Although bacterial counts of their skin are high, infants seem incapable of developing spreading lesions at this time, and their skin lesions are circumscribed and hive-like. The separation at birth withdraws their exogenous sources of hormones and their own levels fall, and only after the third day of life skin lesions become spreading lesions, and progesterone effects apparently predominate. An extremity which was hyperextended in utero can still be hyperextended readily.

By three days of life, Waddell[39] has shown that the normal infant circulates the usual contaminating organisms in his blood stream without being upset by them. Impetigo is common in the nursery period and eczema appears shortly thereafter. The infant's appetite becomes prodigious where it was very little at first. His electrolyte pattern changes, his blood type becomes determinable by simple laboratory methods, and his differential and total count are changed, his breasts enlarge, and female infants may have a vaginal discharge which simulates menstruation. These are all familiar observations of normal infants.

In the morbidity of infancy, the influence of progesterone predominance on calcification may explain tetany of the newborn infant. The influence of the estrogen withdrawal on permeability or integrity of cells may apply to such conditions as subdural hematomata and hemorrhagic disease of the newborn infant, since estrogen withdrawal brings about the menstrual flow and the easy bruising during menstruation is evidence that vessels other than those of the endometrium are affected. The presence of meconium may serve to modify this shock of the sudden withdrawal of the maternal hormones.

Between three days and three weeks of age, while the infant apparently is especially permeable to foods and bacteria, he may develop diarrhea with drastic results. In this disease, diarrhea of the newborn infant, the common bacteria are usually suspected. Breast-fed infants are notably less affected by diarrhea than are artificially fed infants.

Three possible reasons exist for these differences: First, breast milk is high in lactose. Lactose is reputed to facilitate the absorption and deposition of calcium and was reported by Kramer and Lowenburg[40] to induce healing of rickets. Since calcification accompanies other manifestations of the consolidative phase, which include a decrease in cellular and tissue permeability, there may be a physical barrier to the entrance of bacteria. Next, lactic acid, which is produced by the action of the lactobacillus on lactose in breast milk, has a potent effect on the electric resistance of the tissues on which it has been tested. Electric resistance may be important in determining susceptibility of the newborn infant to bacteria.* Thirdly, hormonal assays show that breast milk, like amniotic fluid, is enormously rich in hormones at first, and becomes poorer as time goes on.[42] For a time the nursing infants receive an abundant supply of hormones while those on formulae may not, and in this may lie an explanation for the difference, suspected by mothers and psychologists, between those infants on formulae and those on the breast. The newborn infant is relatively immune to those diseases which are capable of altering the body toward a leukopenia with a relative lymphocytosis, such as measles, mumps and typhoid; he is susceptible to pertussis with its absolute and relative lymphocytosis; his skin is Schick[43] and Dick negative[37] for several months; his major sources of serious infectious difficulty are the organisms of influenza and pneumonia; he develops hemangiomata and he can acquire tuberculosis, and allergies to which he may be subject are associated with exaggerations of permeability.

After the newborn period, the first important change in the estrogen-progesterone relationship on the rhythmic cycle seems to appear at 15 months to 2 years of age. At this age the fat baby body disappears and the infant becomes a child. At this time, too, his prodigious appetite diminishes and he develops enough tone in his muscle that his umbilical hernia disappears. Hemangiomata no longer enlarge. The marked spreading lesions characteristic of early infancy fade in magnitude. Pneumococcic and influenzal meningitis vanish, as does susceptibility to tuberculosis. With them goes eczema. Impetigo will no longer become bullous and scabies will take an adult pattern. He begins to be susceptible to measles, mumps and typhoid and is now extremely susceptible to the high polymorphonuclear leukocytic diseases. He can develop nephrosis and shortly can develop nephritis and rheumatic fever. Meanwhile his mouth epithelium has changed and he can now acquire herpes simplex.

By five or six years his increment of increase in weight is less. His blood count is now approaching the adult pattern, while at his two year node it was at the cross-roads of its change. Again his appetite changes. Physically he becomes a boy and has passed preschool childhood in body and mind. He no longer is a candidate for nephrosis, but is subject to rheumatic fever and to all contagious diseases. His susceptibility to typhoid is more than just perceptible.

The next node on the rhythmic cycle seems to be at nine years of age, which is a latent period before the pubertal spurt. He now begins again to be susceptible to tuberculosis and less so to rheumatic fever. He is past the maximal susceptibility to scarlet

* An additional point of interest concerning lactose was noted by Quilligan.[41] The amount of this sugar in the maternal milk appears to be in approximate proportion to the intelligence of the species. Although intelligence levels are difficult enough to establish even in humans, he points out a possible rationale for the relationship. Lactose reduces to galactose, which combines with the phospholipids to form phrenosin, a galactoside essential to the brain.

fever and diphtheria, as the large Dick and Schick test series indicate. His typhoid susceptibility is still increasing, however, as are his chances for mumps. His blood count is just reaching the adult differential but his hemoglobin and red blood cells are not yet up to adult standards.

It may be of some interest that these nodes can be established on blood pictures, growth patterns and other physiologic bases that are similar for each. This is especially interesting in that these nodes are also the points of significance to psychologists in observations of mental development.

The next phase is, of course, puberty. Here the physical and mental aspects are too familiar to warrant mention. By this age the incidence of positive Dick and Schick tests has now fallen to less than 10% and the susceptibility to mumps and typhoid is at its height. Tuberculosis reaches one of its peaks of incidence and rheumatic fever has a last high spot before it becomes replaced by atrophic arthritis as a disturber of comfort and health.

At the menopausal age these susceptibilities to infectious disease tend to reverse themselves and spreading lesions, like pemphigus, reappear and the contagious diseases become more of a problem.

It seems logical to conclude then, on such a review of the physiologic changes, the accompanying changes in the psychologic state, and in the susceptibility and resistance to disease that a relationship must exist between these states and the coexistent state of the body.

Common Grounds of Diseases

Certain diseases characterized by a relative lymphocytosis have similarities and, in some epidemics, may be quite indistinguishable, while others with a polymorphonuclear leukocyte predomination have other features in common. An example can be supplied. Measles, due to a virus; typhus, to a rickettsia, and typhoid to a bacillus, have similar blood counts, similar tendency to cerebral invasion, similar involvement of skin, gastrointestinal tract and lungs, and a similar pattern of incidence from birth through adult life. In addition they apparently prevent calcification since their occurrence during tooth formation is recorded by a line of inadequate enamel across the teeth. The "spread," the blood count and the effect on calcification all are physiologic concomitants normally and here are increased in degree.

Scarlet fever,* on the other hand, as judged by Dick tests, diphtheria as judged by the Schick test, and meningococcus meningitis as studied in large epidemics of previously unexposed peoples, have a morbidity pattern with the highest incidence of susceptibility before one year of age, then susceptibility falls to the 30 percentile in children from 9 to 10 years of age, and to the 10 percentile at puberty. Each, at the menopause, climbs again. None has a predeliction for cerebral involvement; none involves the lung and gastrointestinal tract characteristically, but all have a high polymorphonuclear leukocyte differential count which suggests a relative inability to spread. These diseases appear to intensify calcification as they leave striations of dense bone across the developing long

* These diseases are also similar in their effects on allergies. Measles, roseola infantum, mumps, chickenpox and Kaposi's disease have a leukopenia but a relative lymphocytosis. Pertussis has an absolute lymphocytosis. These diseases have all been observed by Feingold[44] to increase allergic states in the prodromal period but to relieve them entirely during the height of the disease. The diseases with a polymorphonuclear leukocytosis which he observed have uniformly aggravated the allergies.

bones. There is specificity in each disease, obviously, but apparently there is much common ground. There are intermediate forms such as anterior poliomyelitis, which follow the high polymorphonuclear leukocyte morbidity pattern, but a lymphocytosis is present in the spinal fluid when encephalitic involvement occurs.

Other common ground seems to exist in certain geographic locations for diseases. Panum's[45] well known report on measles in the Faroe Islands surveys the diseases which strike these cold islands. In the pandemic of measles he was studying he found the threshold low for all, but the mortality varied with the age group. He also described epidemic typhoid and typhus, widespread tuberculosis and universal scabies as afflictions of infectious nature, with rheumatic fever in a high proportion of the population. No disease with polymorphonuclear leukocytosis was detected by him. It might be concluded that cold caused a physical reaction which prevented stimulation of polymorphonuclear production, but cold is only one factor.

A warm climate can harbor similar disease patterns. On Guam, Hammon[46] reported that mumps in epidemic form has involved the people, that measles and typhoid are not rare, but that the population, after a few months of age, is immune to streptococcic infections and to diphtheria as evidenced by skin tests, and is serologically immune to anterior poliomyelitis.

These facts suggest that the morphology of the etiologic agent of a disease may be less important than the phase of the individual attacked, and the local pathologic findings cannot be considered to be more than peripheral manifestations of a disease process which disturbs the central controlling mechanism.

These categories of disease are now being investigated to learn whether certain diseases may stimulate growth, as might be anticipated from their similarities to effects of progesterone and estrogen. Evidence for this is already at hand. A child looks thin after an illness. His height-weight ratio has changed from his normal channel; however, he may not have lost weight but, instead, have gained in height.

Metabolic diseases have no etiologic agents detectable by microbiologic methods, but these diseases may be strikingly similar to infectious diseases and may stimulate the same controlling mechanism. Bacterial asthma and dust asthma, for example, are indistinguishable, as are various bacterial and allergic rashes and intestinal upsets. Metabolic disease may also simulate or exaggerate normal physiologic states. The description of a patient with edema, urinary albumin, lethargy, hyperlipemia and some inversion of the A-G ratio would be equally applicable to nephrosis or near-term pregnancy. Thus, apparently widely divergent metabolic states may vary only in degree and the demonstrability of their etiologic agents, and have a common hormonal basis.

Electric Phenomena

To this time the discussion has dealt with familiar physiologic and pathologic phenomena. Now ecologic observations will be introduced and the discussion, largely theoretic in approach, will consider their means of influencing physiologic mechanisms.

Among the direct electric influences exerted upon the earth and its inhabitants are the electromagnetic emanations mentioned earlier, cosmic rays and the more familiar light, with its strikingly opposite poles of violet and red. Then there are the intermediaries which are varied by alterations in the intensity of the fields of these emanations, and which in turn are capable of altering electric fields secondarily. These include temperatures and baro-

metric pressures. Heat, it will be recalled, dissipates magnetic fields and conducts electric energy. Fire reduces the strength of the molecular bond so completely in organic materials that they separate into their original components. Cold allows the maintenance of the magnetic field and the retention of the electric energy.

In these phenomena we have actuators of physiologic function which are applied directly to the body, and also have a potential means of indirect action upon the organism through their effects on terrestrial electric intensity and geomagnetic field. This force may be of considerable significance.

The 28 day cycle which is the most obvious manifestation of periodicity in the human species has its counterparts in the 28 day cycle of the sun's rotation, of the lunar month, and of tree growth, and perhaps of other natural phenomena. It is clear that all women do not menstruate on the same day, but the reappearance of this 28 day interval elsewhere in the biologic world is more than coincidental. Kleitman, in his interest in cycles of various natures, has reported many physiologic phenomena coinciding at least in interval with other natural phenomena, and Burr[47, 48] has followed biologic electric phenomena with the same interest and, from a general point of view, with the same results.

On a daily basis the variations in electric phenomena are less apparent and so also are the physiologic, but the high and low points in the intensity of the electric field during 24 hours appear to correspond reasonably closely with the hours of greatest energy on the one hand, and deepest sleep on the other, in most of mankind. Its usual crest is reached by mid-morning, and its trough by 2 a.m. It was reported in England by Sylvanus Thompson,[49] Professor of Physics at London toward the end of the 19th century, that a secondary rise was to be expected in the early evening and a moderate drop in the late afternoon. He was interested in these determinations as a physicist. A physiologist might have had his curiosity aroused by the correspondence of the two crests of electro-magnetic intensity with those of human energy in mid-morning vigor and mid-evening social, study and sex activities, and again in the troughs by the tea or cocktail hour and sleep.

Since Thompson, the terrestrial fields have been correlated with temperature and barometric fluctuations.[50–53] These latter forces are known to be capable of physiologic reflection but direct effects of terrestrial electric field intensities upon human physiology have remained largely unexplored.[54, 55]

This field should hold promise since the earth and its occupants are constituted of electrons and might logically be expected to respond to forces capable of affecting familiar electronic arrangements. This might seem to apply no more to man than to the soil, but man appears more sensitive to these stimuli as suggested by the similarity of the brain cells to miniature electronic tubes.

An especially convincing study along these lines was conducted and has been published by Wiener[56] as *Cybernetics*. This work demonstrates the similarity of the central nervous mechanism to a complicated series of tubes which store electric impulses, discharge them as the tubes' capacitance is reached, and check the course of their discharge through feedback mechanisms like those in electric computers and in telephonic transmission.

This suggests that the brain may be actuated by the electric fields surrounding the body and the minute fields surrounding each molecule of circulating substance and that dissemination of the impulses from the brain be conducted through contiguous parts, as the hypothalamus, pituitary, and adrenal, to the soma. This speculation does not violate the accepted concepts of the actions of the pituitary nor the recognized inter-

actions of estrogen and the adrenal, nor the facts applying to enzyme systems. It simply raises the question especially concerning the last: Are they primary or are they intermediary nuances, which are recognizable because of the precision of chemistry, but are actually secondary to a primary electric change?

Physiologic functions also may be approached with this thought in mind. For example: the basis of the oxygen-carrying capacity of the red blood cell may be its unique motion and consequent electro-magnetic field. This suggestion is substantiated as follows: (1) The speed of the blood is high in the lung and the arterial circulation, lower in the veins and lowest in the peripheral capillaries. The electro-magnetic fields should vary similarly. (2) Oxygen is strongly paramagnetic and so is attracted by a magnetic field and, as the field diminishes in intensity, is released. It is attracted to the red blood cell in the lung, held in both the venous and arterial vessels, although in different volumes, and released in the peripheral capillaries. (3) Carbon dioxide is weakly diamagnetic and is rejected by a strong electro-magnetic field. (4) Soft iron is responsive to fluctuations in electro-magnetic fields and its curves of magnetization and hyteresis closely resemble oxygen association-dissociation curves. Iron is not utilized by the body in other than oxygen transport mechanisms. It is not metabolized and its intake requirement in the healthy adult male is nil. (5) Cobalt, an essential component of B-12 for blood manufacture, is ferro-magnetic. (6) The sole remaining element of the ferro-magnetic series is nickel which may still be found to be important, especially since cobalt's part is such a recent discovery. This is not critical to the suggestion, since the similarities noted between the chemical characteristics and the physiologic determinations are so striking and all the elements participating in oxygen transfer are those affected by magnetism.

In short, the suggested correlation is as follows: Where the speed of the cells is greatest and the electro-magnetic field would be strongest, oxygen is attracted to the soft iron in the cell and carbon dioxide, repelled by it. In the artery, oxygen is retained but in the peripheral capillary when the speed and field are reduced oxygen is lost and carbon dioxide no longer repelled. In the vein, the field becomes great enough to retain the diminished volume of oxygen and, as in the artery, is not of sufficient intensity to repel the carbon dioxide. In the lung, where the speed and the field are greatly increased, oxygen is further attracted while carbon dioxide is expelled.

As well as to blood, principles of electricity and magnetism can be applied to such phenomena as permeability of cells and to cellular division and integrity. It is interesting, too, to regard the chemistry of the hormones from this point of view.

Their molecules are constituted basically of a cyclopentenophenanthrene ring. To this basic structure, estrogen has only an oxygen, a methyl, and a hydroxyl group attached. Since estrogen appears to be the chemical concomitant of increased electric intensity, perhaps in a relatively strong field hydroxy-carbons are not available to the ring for prosthetic groups but are tightly held to their original molecules and, as a result, the cyclopentenophenanthrene ring exists with minimal attachments. If the intensity of the field were diminished, other groups might be released from other molecules and become attached to the ring, and progesterone would be the result.

Another link in this hypothetic chain would be androgen, the "male sex hormone." This molecule has the same basic ring with a longer prosthetic group than estrogen. Structurally it lies between estrogen and progesterone. In the chemical laboratory it occupies this same position in the conversion of cholesterol to progesterone to estrogen. Physiologically, Selye's[57] work demonstrates that in animals it functions as estrogen, then as progesterone, according to the amounts administered, before it assumes an individuality

of its own. It becomes detectable on excretion when the other two hormones are high in quantity. It, too, is present in both sexes. Its action can be characterized as the stability factor; and its analogy, in the terms used to describe progesterone as heat and estrogen as a bright cool morning, is cold. The leafless tree in winter, which neither progresses nor retrogresses, exemplifies this nature of stability.

The final link and apparent source of this chain is cholesterol. This substance is common to all cells of higher animals and has close chemical parallels in the lower animals and plants. Chemically it is based on the same ring and has a still longer prosthetic group than has progesterone. Physiologically it varies inversely with estrogen's degree of predominance. Its action would be characterized as inertia.

Much of this last, obviously, is speculative.

Summary and Conclusions

A study has been made of the known phenomena which affect the biologic organism. Certain correlations have been found and other correlations are logically inferred. The common grounds of anatomic structures, the anatomic responses to endocrine stimuli, the interrelationships and interdependencies of the endocrines and external stimuli have been followed and have been related to cellular permeability and hyaluronic acid. Cellular phases, including the rhythmic alternations in physiologic functions, have been delineated and their importance stressed. Further, the probability is advanced that this rhythmicity originates physiologically in the brain but that the brain itself is capable of receiving transmissions from within and without the body, and disseminating them, again rhythmically, in normal or altered amplitude and frequency.

Further experimental evidence of these correlations and their practical extrapolations into drug actions and the therapy of infections and metabolic disease will be reported and will include clinical, animal and *in vitro* studies.

At present, the following conclusions seem justified:

1. No component of the body is capable of independent action.
2. Action in any component is reflected, according to its magnitude and directness of application, upon all the body.
3. All such actions are mediated by the brain.
4. There is a dynamic, rhythmic cyclicity in physiologic action which can be altered in amplitude and frequency.
5. These rhythms are alternations of cellular tenseness and relaxation.
6. The concomitants of the tense phase are compactness, impermeability, electric conductivity and contraction of all cells, and these characteristics might be described collectively as the factors operative in maturing the cell. The concomitants of the relaxed phase are laxness, permeability, electric resistance and expansion of all cells and are factors of growth.
7. The phase of tenseness is accompanied by an increase in certain hormonal activities and that of relaxation by an increase in others.
8. The hormones may be causes of the phase or the results of it.
9. Infectious disease cannot act as an extraneous agent capable of bringing its own engine into such a highly integrated mechanism but must act on the body through its ability to affect one of the body's mechanisms.
10. Drugs must act through the same channels available to disease.

11. Foods may contain, in addition to their caloric content, components capable of stimulating either the phase of cellular expansion or cellular compaction, particularly foods from the reproductive systems of plants or animals (milk, eggs, cereal, for example).

12. Vitamins each stimulate one phase and should be evaluated in terms of positive actions.

13. Inherent growth and maturation factors are not of fixed capacity in an individual but beyond certain limits must be supplied him or applied to him constantly.

14. The hormone most manifest in the tense phase is estrogen and so may be considered the maturation factor, and the one most manifest in the phase of relaxation or cell division is progesterone, which may be considered the growth factor.

Acknowledgment

Acknowledgment of my debt and thanks are due so many for their support and assistance in one or another aspect of this work that I regret all cannot be mentioned. However, to members of the Staff of The Children's Hospital of Philadelphia and in particular Joseph Stokes, Jr., T. F. McNair Scott, Milton Rapoport, Lewis N. Barness and Audrey Bill, to E. B. Krumbhaar, A. N. Richards and John Hubbard, and to Giden K. deForest, to J. J. Quilligan, to the S. Y. Gibbons, to the S. E. Longmaids, to J. W. Manchly, to Warren and Pauline Berry Mack and to my daughter, Cornelia, I owe too much to fail to acknowledge it. At the same time, I want to make it entirely clear that my debt to them in no way involves them and that the paper "does not necessarily express the opinion" in any part, of any of them.

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INTERNATIONAL NEWS

NEWS FROM ENGLAND

RICHARD W. B. ELLIS, M.D., *Corresponding Editor*

The North-Eastern Region of Scotland has had a culture of its own that extends back to prehistoric times. It is also circumscribed geographically and is well adapted for the regionalisation of the child health services. The Region is now one of the five into which Scotland is divided for the purposes of the National Health Service (Scotland) Act, 1947; and, as determined by the Secretary of State, the area in which the North-Eastern Regional Hospital Board "exercises functions with respect to the administration of the hospital and specialist services" consists of the City of Aberdeen; the Counties of Kincardine, Banff and Moray; and, in the far north, the island counties of Orkney and Shetland. All the hospitals in the Region, teaching and nonteaching alike, come under the Regional Hospital Board, which in turn appoints Boards of Management for groups of hospitals under a scheme approved by the Secretary of State.

In the City of Aberdeen, the only large burgh in the Region, the Board of Management for the Special Hospitals controls the Royal Aberdeen Hospital for Sick Children, the Maternity Hospital and the City (Fever) Hospital. It will be seen at a glance that such a grouping is admirably suited to the needs of the child health service, for all the hospitals concerned with infants and children are under one Board and one Medical Superintendent, with the exception of a home for mentally defective children. In accordance with the Act, the hospital and specialist services are provided in association with the University of Aberdeen and its School of Medicine.

The population of the Region in 1948 was 505,700, of whom 188,853 were in Aberdeen City; 116,728 were in small burghs and 200,119 were in landward areas. Of the half-million inhabitants, about 125,000 were children. In 1948 the total live births in the Region were 19.7/1000 population. There were 273 stillbirths. The deaths under 15 years of age were 472, of whom 36 infant deaths/1000 live births were in the first year of life, 53 were at ages 1 to 4 and 62 at 5 to 14 years.

In Aberdeen City are the main hospitals for the care of children. The Royal Hospital for Sick Children, founded in 1877, was moved in 1929 to new buildings, the first to be erected on the common hospital site at Foresterhill on the outskirts of the city. On this site also now stand the Medical School of the University, the Maternity Hospital, the large general hospital and the Students' Hostel. The Children's Hospital has 150 beds of which 48 are set apart for medical cases. Next year there will be opened a new pavilion now being built that will take 12 mothers along with their babies, and 20 other babies, all in separate cubicles. The Maternity Hospital has 40 beds and a labour unit, an antenatal block of 28 beds and a sick nursery of 30 cots. Elsewhere in the city are three auxiliary homes for 51 cases. The City (Fever) Hospital of 250 beds has a ward of cubicles that can take 18 infants with diarrhoeal diseases; and in other wards and rooms are varying numbers of children with zymotic diseases, pneumonias and other acute conditions, and with tuberculosis. There are scattered over the Region smaller hospitals, mainly of the cottage type, that altogether have 164 maternity beds. Just outside the City of Aberdeen is a home for 50 mentally defective children. There is space for extension of this home and at least two hundred extra beds are required.

The active paediatric staff of the Region is provided by the professorial unit, and consists of three consultants, the Professor of Child Health, the Lecturer in Child Health (full time University appointments) and a full time Physician; four Registrars (physicians in training); and four clinical assistants (of whom three are Child Welfare Officers who help in the outpatient department of the Children's Hospital). Included in the duties of the medical staff are responsibilities for the care of medical cases in the Children's Hospital, ill and well babies in the maternity hospitals, and all infants and children under 12 years of age in the fever hospital. One of the consultants is available, on request, to see patients in their own homes in consultation with any family doctor. These are called "domiciliary visits," and are provided free under the National Health Service scheme. The professor pays visits (once or twice a year) to the Orkney and Shetland Islands, where he is available to see cases in consultation, and where he meets the doctors, district nurses and health visitors, and usually gives them a talk of paediatric and topical interest.

School Medical Services and Child Welfare ones are provided by the local government authori-

ties—the town and county councils. Most of the burghs have (under the Medical Officers of Health) an infant welfare clinic, conducted by Child Welfare Officers in the majority of cases and by family doctors in only a few. The whole Region is well served by devoted bands of district nurses and health visitors, with a nursing superintendent for each county. Special schools for mentally backward, and physically handicapped and for deaf children exist in the City of Aberdeen, but elsewhere in the Region there are none. There is a clamant need for beds for mentally defective children who require institutional care. Child guidance is well covered by the Professor of Mental Health and his staff. For children "deprived of a normal home life," provision has to be made under the Children Act, 1948, and already two homes have been provided for such children in the City of Aberdeen and one in the County of Aberdeen.

There are quite a number of voluntary homes for healthy children who are orphaned, and there is a home for unmarried mothers and their babies—all in the city or near it. Various social service organisations help children in many ways such as providing clothing and footware, babies' outfits and blankets, and giving short holidays at a country home.

The teaching of paediatrics is done at the three main hospitals (children's, maternity and fever) by the Professor and all the medical staff. Altogether the students get 130 hours of active instruction in the health and diseases of the newborn, infants, and older children in the form of lectures and teaching clinics. The Regional Maternity and Child Welfare Officer gives lectures in her subject and takes the students to her baby clinics.

There is excellent co-operation in the Region between the paediatricians of the hospital services and the medical officers of health, so that the curative and preventive paediatric services can work together towards their common aim, the betterment of the lives and health of the children in the Region. More and better buildings are required for many of the services, although Aberdeen was fortunate in having new main hospitals built on the common hospital site in the years before the second Great War. As I said in a recent survey,* although some "new buildings will be long in coming, we can take comfort in the thought that the doctors and nurses and their helpers are more important than the walls within which they work. We can all help the children by striving to improve our teaching and our thinking, and by doing these two things with more imagination."

JOHN CRAIG, M.B., CHB., F.R.C.P.E.
Professor of Child Health
University of Aberdeen

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* Paediatrics in the North-Eastern (Aberdeen) Region of Scotland, 1950. (Privately printed by Aberdeen University Press.)

NEWS AND ANNOUNCEMENTS

The American Pediatric Society will hold its next meeting on May 2, 3 and 4, 1951, at the Traymore Hotel, Atlantic City, Dr. Henry G. Poncher, Secretary.

* * *

The next meeting of the Society for Pediatric Research will be held on May 2 and 3, 1951, at the Traymore Hotel, Atlantic City, Dr. Robert Ward, Secretary.

* * *

Dr. Bertram R. Girdany, formerly of Babies Hospital in New York, has joined the Pediatric Staff of Children's Hospital of Pittsburgh as Physician-in-charge of the X-ray Department. This appointment also carries teaching responsibilities in the Department of Pediatrics of the School of Medicine of the University of Pittsburgh. Dr. Girdany assumed his new position on Dec. 1, 1950.

* * *

The following diplomates were certified by the American Board of Pediatrics, Inc.:

Boston—Dec. 1, 2 and 3, 1950

Alford, Hyman, 1755 Beacon St., Brookline, Mass.
Barness, Lewis A., Warrington, Bucks County, Pa.
Bell, William Randal, 36 Locust St., Marblehead, Mass.
Brazelton, Thomas Berry, 51 Brattle St., Cambridge, Mass.
Browning, William M., 3740 Central Ave., Indianapolis
Christian, Joseph R., 414 S. Oak Park Ave., Oak Park, Ill.
Clarke, Gene Hofmeister, 2300 Main St., Buffalo
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Drucker, John J., 75 Ascan Ave., Forest Hills, N.Y.
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The next Oral Examination will be at New Orleans, March 2, 3 and 4 ,1951.

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Dr. Philip R. Miller, Brooklyn, died on Dec. 23, 1950. He was a fellow of the American Academy of Pediatrics.

Segundo Curso de Pediatría y Puericultura. Abril 16-28, 1951 Universidad de Santiago de Compostela, España

El lunes 16 de abril, 1951, comenzará el Segundo Curso de Ampliación de Pediatría y Puericultura, organizado por la Cátedra de Pediatría de la Universidad de Santiago de Compostela y Escuela de Puericultura de Galicia, dirigido por el profesor Dr. Manuel Suarez y colaboradores. La primera semana se dedicará al estudio de los problemas de Hematologia Infantil y la segunda a temas de Actualidad Pediatrica, tales como: el tratamiento de las cardiopatías congenitas, terapeutica hormonal en pediatría, avances y profilaxis de enfermedades infecciosas y otros. El curso incluye la presentación diaria de casos clinicos, asi como practicas especiales de laboratorio, cocina dietetica, radiodiagnostico, y tecnicas diagnosticas y terapeuticas. Para informacion e inscripciones: Catedra de Pediatría. Facultad de Medicina. Santiago de Compostela. España.

BOOK REVIEWS

THE CHEMISTRY AND PHYSIOLOGY OF GROWTH, J. H. Northrop, F. O. Schmitt, K. V. Thimann, K. Folkers, C. B. Van Niel, E. S. G. Barron, P. Weiss, J. S. Nicholas, C. P. Rhoads, and C. N. H. Long, edited by A. K. Parpart, Princeton, N.J., Princeton University Press, 1949, $4.50, 293 pp.

This interesting book is an outgrowth of a conference on "The Chemistry and Physiology of Growth," held at Princeton in September 1946. The arrangement by Dr. Parpart of the contributions from each of the 10 participants has resulted in an orderly and absorbing account of both current knowledge and future problems to be solved in this field.

Considering that proteins form the major structural components as well as the organic catalysts of living cells, Northrop's opening chapter on "Enzymes and the Synthesis of Proteins" forms a logical starting point for the book. He begins with the statement that "any hypothesis purporting to account for the synthesis of proteins by means of enzyme reactions must conform to the general theory of catalysis." Northrop then discusses, in successive sections of the chapter, (1) Catalysis, (2) Formation of Normal Proteins, (3) Formation of Viruses, (4) Formation of Adaptive Enzymes, (5) Formation of Antibodies. Not the least valuable part of this chapter is the well-chosen bibliography of 137 titles.

In the second chapter Schmitt deals with the problem of morphology at the molecular level. He describes our current knowledge of the structure of the protein molecule—its internal architecture—together with theories of its genesis and the relation between the molecule's structure and its environment. In closing, Schmitt points out that "the chromosome is, of course, the final and best illustration of the importance of macromolecular ecology. On this structure is imposed the task not only of maintaining through countless duplications a rigid structural integrity . . . but also of presiding over the multitudinous determinative processes of growth and development."

Chapters III and IV by Thimann and Folkers deal with the factors which determine the mass and direction which these structural units acquire in the growing organism. "Plant Growth Hormones" and "Unidentified Vitamins and Growth Factors" are the titles of these 2 chapters which give the reader a picture of the different factors active in plant and animal organisms. Folkers' chapter should be of interest to pediatricians because of its very complete review of the work on folic acid and the whole group of possibly chemically related growth factors.

Van Niel, in Chapter V, considers "The Kinetics of the Growth of Micro-organisms." He points out that even though micro-organisms seem like rather simple structures "nevertheless they display an astonishing diversity of functions which in many respects they share with the trees, oysters, butterflies, and elephants." From their environment they pick up a variety of chemical compounds and convert them into cellular constituents. The cell thus grows and divides to produce more cells in which the existing pattern is exactly duplicated. Growth is "the expression par excellence" of the dynamic nature of living organisms. Thus a study of the microbial growth curves becomes of importance in gaining a better understanding of the mechanisms whereby synthesis of the chemical compounds leads to growth. Van Niel reviews the studies of microbial growth.

What starts and maintains this dynamic process which leads to growth? The sixth chapter by Barron on "Cellular Metabolism and Growth" deals with this question. He notes that the synthesis which predominates in dividing and growing cells "is provided by enzymatic reactions largely of the oxidation-reduction type." Thus the first part of this chapter presents a discussion of oxidation-reduction systems of the organism. Later Barron takes up Regulatory Mechanisms, Cell Division, and Cell Growth. He includes a bibliography of 89 titles.

Weiss, in Chapter VII, discusses the whole complex question of the differentiation of cells during growth, under the title "Differential Growth." Here the physician interested in growth will find much food for thought. Many bits are worth quoting for the sake of intriguing the pediatrician—a few must suffice. "There can be no research on growth as such. We can only study growing objects." "We realize now that any factor that has an effect on the physico-chemical setting in

which growth occurs may thereby alter the manifest form which the growth process will take. But it is evident that such actions will be in the nature of merely modifying already established patterns rather than instituting wholly new ones." "Growth is not a simple and unitary phenomenon. . . . To deal with growth as an entity which can be 'activated,' 'stimulated,' 'retarded,' or 'suppressed' is only part science, and for the other part, fiction." "The less we let our work and thoughts be misled by the delusion that growth is basically but a simple elementary process . . . the faster will be our progress toward true insight into the real mechanisms of development." Sixty references are appended to this chapter.

"Problems of Organization" occupy the eighth chapter written by Nicholas. As he points out, the problem of how the developing egg gives rise to the structures of the adult is a very old one. His discussion of recent work (87 references) on this process of organization covers the following topics: Nucleocytoplasmic Relationships, Egg Constituents, Organizational Dependencies, Independent Movements, Mass Movements in Organization, Chemical Organization, and Regeneration.

The ninth chapter by Rhoads is on "Neoplastic Abnormal Growth." This contains less stimulus for the student of child growth than the 2 preceding chapters even though the physician may find its language a little more familiar. Moreover, many practitioners will be interested in the immediate applications of the newer knowledge of cellular growth to clinical cancer problems. There are also interesting discussions of relationships between genes and viruses, between mutations and the development of cancer cells, and of the inheritance of cellular traits. The author has included 126 references.

The final chapter is by C. N. S. Long on "The Adrenal Gland, a Regulatory Factor." In these days of continued excitement over the actions of ACTH and cortisone we need hardly urge the reader to avail himself of this beautifully written essay on the functions of the adrenal gland.

The reviewers feel that this is a most worth while book for any one interested in almost any aspect of growth. It is certainly to be recommended to all pediatricians who still consider themselves postgraduate students, eager to gain more understanding of growth.

SHOCK AND ALLIED FORMS OF FAILURE OF THE CIRCULATION, H. A. Davis, M.D., C.M., F.A.C.S., New York, Grune & Stratton, 1949, $12.00, 595 pp.

Essentially, this volume is an exhaustive review of the world literature on the laboratory and clinical investigations of shock, and as such constitutes an excellent reference text. As indicated by the title, the author's interest is oriented around the circulatory aspects of shock. He provides a "biologic definition of shock" as a ". . . generalized impairment of the circulation caused by any form of stress or injury which reduces the output of blood from the left ventricle of the heart to a level below that needed for normal cellular function and metabolism." Whereas such a definition may seem too restrictive in concept to many physiologists, it should be pointed out that there are detailed considerations of the pathologic physiology, pathology and pathogenesis of shock and shock-like states. The subject of traumatic shock receives the greatest amount of attention, but there are chapters on shock associated with toxemias and infections, diseases of the liver, burns, anesthesia and thoracic disturbances. Also included is an excellent chapter on the treatment of circulatory failure, with certain brief considerations of pediatric technics.

In discussing Selye's concept of the alarm reaction, with its shock and counter shock phases, the author objects, among other things, to what he interprets as Selye's belief that different forms of stress act in different ways on the organism. It is the reviewer's understanding that Selye's concept arose from observations of an exactly opposite character, namely, that so many different forms of stress seemed to evoke essentially the same pattern of response or adaptation. The author, in turn, offers what he calls "the concept of triphasic response to stress" which bears considerable resemblance, at least superficially, to Selye's concept, and in which anoxic injury is the basic disturbance.

The book is well documented with over 2200 references. There are 55 illustrations and photographs and 17 tables.

EDITORIAL

POSTINOCULATION POLIOMYELITIS

POLIOMYELITIS following immunizing injections of presumably sterile material has occasionally been reported since 1921,[1-5] as well as after Jennerian vaccination,[6-8] but until quite recently the occurrence has been considered so rare as to have little practical significance. The publication in 1950, however, of four papers, three from England (London)[9-11] and one from Australia,[12] in which about 100 cases of this sort were reported, nearly all in young children, and of an editorial in the *Journal of the American Medical Association*[13] has suddenly increased interest in the subject and made it a matter of general concern to practicing physicians, particularly pediatricians.

Martin[9] of London in March 1950 recorded 17 cases occurring in the period 1944-49, all under 3 years of age, in which paralysis of the inoculated limb began, with one exception, between 8 and 28 days (average, 17 days; median 16 days), after injection. In April 1950, McCloskey[12] of Melbourne, Australia, reported 29 cases in children of 1 to 15 years (25 under 5 years) of poliomyelitis beginning 4 to 32 days after inoculation (average 13 days; median 12 days), in 24 of which paralysis developed in the inoculated limb. In April 1950, Geffen[10] reported 30 cases from London in which paralysis of the inoculated limb began less than 29 days after inoculation; in the same area and year, 182 cases of poliomyelitis, presumably including the 30 postinoculation cases, were reported. In July 1950, Hill and Knowelden[11] reported, also from London, 40 cases in children under 5 years with paralysis beginning 8 to 28 days (80% of them, 8 to 17 days) after injection, of which 33 showed involvement of the inoculated limb. During the same period (1949) in the same area of notification and age group, a total of 410 cases of poliomyelitis were reported. This series probably includes part or most of Geffen's cases; both showed a startlingly high proportion of all poliomyelitis cases related to recent injections. In the four reports, the interval between injections and the onset of symptoms was less than five days in only three instances.

No one type of inoculum was exclusively implicated. While alum-precipitated diphtheria toxoid (APT), pertussis vaccine or mixtures of the two were used in most instances, similar effects have followed penicillin,[4,5,9] typhoid-paratyphoid vaccine (TAB),[2,4,5] cholera vaccine[1] and, as already mentioned, smallpox vaccination.

The diagnosis of poliomyelitis in the reported cases appears to have been reasonably certain. The clinical features, including early and residual flaccid paralysis, have been typical as have the examinations of cerebrospinal fluid. The absence of characteristic sensory symptoms and signs appears to rule out neuritis. The fatality rate seems to have been low, and no postmortem studies appear in the four reports, but MacCallum[14] reported recovery of poliomyelitis virus from the stools of five postinoculation cases, two of them with paralysis of the injected limb.

Martin, McCloskey and Hill and Knowelden have mentioned certain possible explanations for the injection-poliomyelitis sequence, none of which they regard as altogether satisfactory. Considering the variety of materials implicated, the lack of correlation with particular batches of material, and the stringent regulations for commercial manufacture of biologic materials, it seems virtually impossible that the supplies themselves had been contaminated with poliomyelitis virus. All three papers favor, though with reservations, the theory that the patients harbored latent infection at the time of injection and

that the trauma produced by the injected materials promoted both the conversion of latent into apparent infection and its localization in the inoculated limb. This theory was based largely on the reports of Russell[4,5,15] and of Hargreaves[16] in which severe physical activity tended to produce or to increase paralysis, sometimes in the limb subjected to the greatest stress (postexertional type). Another possible explanation suggested by McCloskey but regarded by him as improbable is that syringes or needles used for injections may have been accidentally contaminated with the virus, from the doctor's hands, the patient's skin, or from other patients on whom they had been used, assuming inadequate sterilization thereafter.

The practical importance of finding the correct explanation is obviously so great that further exploration of the subject is urgently needed. However, facts already established but not brought out or sufficiently emphasized in previous discussions may provide the means of clarifying the issue and bringing it near solution.

Basically, poliomyelitis is a nerve-transmitted infection[17] and it has been abundantly proved that if the virus is introduced into peripheral nerve[18,19] it will travel centripetally to the nerve cells of the latter and, reaching the central nervous system, infect the corresponding motor segment of the spinal cord or brainstem, producing a primary paralysis referable to that segment. We have found[20] this process to occur also after direct introduction of virus into voluntary muscle (face, arm), presumably because the exposed motor nerves afford a direct pathway for ascent of virus from the muscle to the regional motoneurons. It is noteworthy that in everyday practice, many and perhaps most immunizing and other injections (e.g., penicillin) into the arm, buttock or leg, are actually intramuscular, often intentionally so. Experimentally, it has been repeatedly[21–25] shown that intra- and subcutaneous inoculations of poliomyelitis virus are also frequently, if irregularly, followed by paralytic poliomyelitis. While, unfortunately, none of the published experimental studies has specified the site of the initial paralysis and only one the site of inoculation, it is perhaps not unreasonable to anticipate the existence of a relationship between the two after exposure of the cutaneous nerves; indeed, certain human experiences, to be presently cited, corroborate the expectation.

To see whether the mechanism just discussed furnishes a clue to the human problem of postinoculation poliomyelitis, it will be helpful to divide the reported cases following trauma and stress into two groups: Group I, those in which the disease has followed penetrating trauma; and Group II, those in which it has followed simple physical stresses uncomplicated by penetrating trauma. Scrutiny of the various case reports in the light of these criteria reveals significant differences between the two groups, particularly as regards the interval between the trauma or stress and the onset of symptoms and/or paralysis. Thus, in the four reports of postinoculation poliomyelitis, the intervals with only exceptions fell within the recognized incubation period, 3 to 35 days,[26] of poliomyelitis in general, whereas in the reports of Russell and of Hargreaves the interval was generally less than four days, and in Horstmann's[27] more recent study, no effect of physical stresses in promoting paralysis appeared unless the patient already showed poliomyelitic symptoms. Another example of Group I is presented by post-tonsillectomy poliomyelitis in which paralysis is also usually segmental (bulbar) to the trauma and in which, as shown by Aycock's[28] study, the incubation period is nearly always between 6 and 30 days. It seems clear that in Group I, with rare exceptions,* there has

* In the 4 series of postinoculation poliomyelitis, only 2 patients can definitely be said to have been harboring infection at the time of inoculation. Patient No. 11 of Martin's series developed

been no evidence of poliomyelitic infection prior to the trauma, while in Group II, the reverse is true. It is interesting to note that in Russell's last paper,[4,5] dealing mainly with Group II, Group I is represented by two cases, one after typhoid vaccine and one after penicillin, both with segmental paralysis, in which incubation periods of 7 and 8 days, respectively, were noted, with paralysis 3 and 4 days later. The segmental localization of paralysis appears to be much more frequent and well-defined in Group I than in Group II. Thus, in Hill and Knowelden's series with onset 30 days or less after inoculation, segmental paralysis occurred in 33, or 80% of cases. As regards Group II, Horstmann was unable to state with certainty in her series whether localization actually occurred in relation to the region of maximum stress, while Russell[45] notes such a relationship in only 9 of the 100 patients studied by him; both authors stress the importance of severe exertion in favoring or increasing paralysis, rather than its localizing effects. Experimentally, Levinson, Milzer and Lewin[29] were unable to localize paralysis by nonpenetrating trauma applied to monkeys during the preparalytic stage of infection.

From the facts just presented, the possibility must be seriously entertained that in cases of Group I, virus has been accidentally introduced by injection or other forms of penetrating trauma, presumably into superficial nerves. There is other evidence to support this view. On the basis of a fairly uniform rate of progression of poliomyelitis through peripheral nerve—$\pm$2.4 mm./hour[50]—the incubation period, which measures the time required for the virus to reach the central nervous system and produce symptoms, should be shorter for injections into the arm than into the leg. In the cases reported by McCloskey, this expectation is fulfilled to the extent that the average incubation period for arm injections was 11.2 days (median, 11 days), and for leg injections, 17.7 days (median, 14 days). The experimental reproduction of postinoculation poliomyelitis has already been cited. There is a human counterpart to this in the tragic results in 1935-36 of attempted immunization with active poliomyelitis virus, putatively attenuated with sodium ricinoleate.[37] As reported by Leake,[32] nine cases of poliomyelitis, all with segmental paralysis, followed cutaneous injections of this material ("vaccine A"), the median incubation period being 10 days after the first or only injection. Excepting for their high fatality rate, these cases appear to have been identical with those presently under consideration.

If postinoculation poliomyelitis results from introduction of virus at the time of injection, the source of virus might be one or both of those mentioned by McCloskey: (1) the skin of the patient; (2) the syringe or needle, or possibly the container of the biologic material used, contaminated in one way or another and not fully sterilized. The available data give no clue to which of these is the actual source. Most of the cases have occurred during epidemics when virus is presumably widely disseminated and could readily contaminate both persons and objects. Experiences with serum hepatitis[33-36] shows the dangers of transmission by needles and syringes incompletely sterilized and the considerable difficulty in practice of attaining complete sterilization of syringes and needles, for which autoclaving is now generally regarded as the safest method. The respective resistances to heat of the viruses of serum hepatitis and of poliomyelitis are,

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symptoms on the day of inoculation and paralysis in the same limb on the next day. In one of Hill and Knowelden's cases, paralysis began one day after inoculation but not in the same limb. The only other case with an incubation period of less than 5 days was one of McCloskey's series in which paralysis in both legs began 4 days after inoculation in both legs. However, 4 days is within the normal incubation period of poliomyelitis.

in fact, not too dissimilar. The former is said to withstand exposure to 56°C. for 60 minutes,[37] while the latter, according to the recent study of Lawson and Melnick,[38] requires over 60°C. for 30 minutes for complete inactivation, and in protein-containing media higher and more prolonged exposures for both appear to be necessary (60°C. for 10 hours for hepatitis virus in albumin; 5 to 10° extra for polio virus in milk). Since, in contrast to serum hepatitis, the virus of poliomyelitis is rarely present in the blood,[39] it may be surmised that the source of infection in postinoculation poliomyelitis is not blood or its derivatives.

In summary, poliomyelitis following inoculations of immunizing materials of various sorts, with paralysis in the inoculated limb may be due to accidental introduction into peripheral nerves of virus from the patient's own skin (perhaps the more likely explanation), or from previously contaminated needles or syringes inadequately sterilized, rather than to exacerbation and localization of pre-existent infection. This conclusion is based on the following observations: (1) the onset of symptoms and paralysis has regularly occurred after an asymptomatic interval corresponding with the established incubation period of poliomyelitis; (2) the mean and median intervals appear to be longer for injections into the leg than into the arm in harmony with the greater length of peripheral nerve to be traversed by the virus; (3) the cases appear to be identical in essentials with those following immunizing injections of virus known to have been in active form; (4) the same picture has been experimentally reproduced in monkeys by inoculation into peripheral nerve, as well as into muscle.

The following practical suggestions emerge from the foregoing discussion as of potential preventive value:

1. Syringes and needles used for injections of all sorts should be sterilized by autoclaving; or, if this is impractical, by boiling for 20 minutes.

2. A strong antiseptic should be used, preparatory to injections, both on the patient's skin and on the stopper of the vial. Alcohol or soap and water cannot be regarded as safe. Until more information is available as to the antiseptic of choice, 2% tincture of iodine is suggested.

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symptoms on the day of inoculation and paralysis in the same limb on the next day. In one of Hill and Knowelden's cases, paralysis began one day after inoculation but not in the same limb. The only other case with an incubation period of less than 5 days was one of McCloskey's series in which paralysis in both legs began 4 days after inoculation in both legs. However, 4 days is within the normal incubation period of poliomyelitis.

in fact, not too dissimilar. The former is said to withstand exposure to 56°C. for 60 minutes,[37] while the latter, according to the recent study of Lawson and Melnick,[38] requires over 60°C. for 30 minutes for complete inactivation, and in protein-containing media higher and more prolonged exposures for both appear to be necessary (60°C. for 10 hours for hepatitis virus in albumin; 5 to 10° extra for polio virus in milk). Since, in contrast to serum hepatitis, the virus of poliomyelitis is rarely present in the blood,[39] it may be surmised that the source of infection in postinoculation poliomyelitis is not blood or its derivatives.

In summary, poliomyelitis following inoculations of immunizing materials of various sorts, with paralysis in the inoculated limb may be due to accidental introduction into peripheral nerves of virus from the patient's own skin (perhaps the more likely explanation), or from previously contaminated needles or syringes inadequately sterilized, rather than to exacerbation and localization of pre-existent infection. This conclusion is based on the following observations: (1) the onset of symptoms and paralysis has regularly occurred after an asymptomatic interval corresponding with the established incubation period of poliomyelitis; (2) the mean and median intervals appear to be longer for injections into the leg than into the arm in harmony with the greater length of peripheral nerve to be traversed by the virus; (3) the cases appear to be identical in essentials with those following immunizing injections of virus known to have been in active form; (4) the same picture has been experimentally reproduced in monkeys by inoculation into peripheral nerve, as well as into muscle.

The following practical suggestions emerge from the foregoing discussion as of potential preventive value:

1. Syringes and needles used for injections of all sorts should be sterilized by autoclaving; or, if this is impractical, by boiling for 20 minutes.

2. A strong antiseptic should be used, preparatory to injections, both on the patient's skin and on the stopper of the vial. Alcohol or soap and water cannot be regarded as safe. Until more information is available as to the antiseptic of choice, 2% tincture of iodine is suggested.

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